

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
11 May 2006 (11.05.2006)

PCT

(10) International Publication Number
WO 2006/048754 A1

(51) International Patent Classification⁷: **C07D 235/08**,
401/06, 403/06, 405/06, 413/06, 471/04, A61P 37/08,
11/06, 1/04, A61K 31/4184 // (C07D 471/04, 235:00,
221:00)

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Chita-gun, Aichi-ken 470-2393 (JP).

(21) International Application Number:

PCT/IB2005/003325

(22) International Filing Date: 19 October 2005 (19.10.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

| | | |
|------------|------------------------------|----|
| 60/624,578 | 2 November 2004 (02.11.2004) | US |
| 60/696,358 | 30 June 2005 (30.06.2005) | US |

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

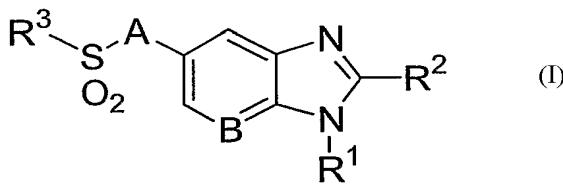
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SULFONYL BENZIMIDAZOLE DERIVATIVES



(57) **Abstract:** This invention relates to compounds of the formula (I) or a pharmaceutically acceptable salt thereof, wherein A, B, ^{R1}, ^{R2} and ^{R3} are each as described herein, and compositions containing such compounds, and the use of such compounds in the treatment of a condition mediated by CB2 receptor activity such as, but not limited to, inflammatory pain, nociceptive pain, neuropathic pain, fibromyalgia, chronic low back pain, visceral pain, acute cerebral ischemia, pain, chronic pain, acute pain, post herpetic neuralgia, neuropathies, neuralgia, diabetic neuropathy, HIV related neuropathy, nerve injury, rheumatoid arthritic pain, osteoarthritic pain, back pain, cancer pain, dental pain, fibromyalgia, neuritis, sciatica, inflammation, neurodegenerative disease, cough, broncho constriction, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), colitis, cerebrovascular ischemia, emesis such as cancer chemotherapy-induced emesis, rheumatoid arthritis, asthma, Crohn's disease, ulcerative colitis, asthma, dermatitis, seasonal allergic rhinitis, GERD, constipation, diarrhea, functional gastrointestinal disorders, irritable bowel syndrome, cutaneous T cell lymphoma, multiple sclerosis, osteoarthritis, psoriasis, systemic lupus erythematosus, diabetes, glaucoma, osteoporosis, glomerulonephritis, renal ischemia, nephritis, hepatitis, cerebral stroke, vasculitis, myocardial infarction, cerebral ischemia, reversible airway obstruction, adult respiratory disease syndrome, COPD, cryptogenic fibrosing alveolitis and bronchitis.

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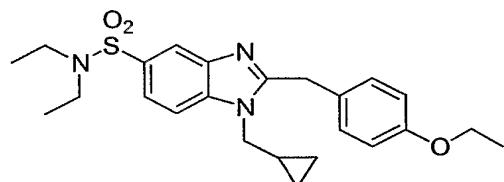
Sulfonyl Benzimidazole Derivatives

Background of the Invention

This invention relates to sulfonyl benzimidazole derivatives. These compounds have selective cannabinoid(CB)2 receptor agonistic activity. The present invention also relates to a pharmaceutical composition, method of treatment and use, comprising the above derivatives for the treatment of disease conditions mediated by CB2 receptor activity; in particular CB2 receptor agonistic activity.

In general, CB2 receptor agonists are found to be useful for the treatment of a variety of diseases, including inflammatory pain, nociceptive pain, neuropathic pain, fibromyalgia, chronic low back pain, visceral pain, rheumatoid arthritis, Crohn's disease, ulcerative colitis, asthma, dermatitis, seasonal allergic rhinitis, gastroesophageal reflux disease (GERD), constipation, diarrhea, functional gastrointestinal disorder, irritable bowel syndrome, cutaneous T cell lymphoma, multiple sclerosis, osteoarthritis, psoriasis, systemic lupus erythematosus, diabetes, glaucoma, osteoporosis, glomerulonephritis, renal ischemia, nephritis, hepatitis, cerebral stroke, vasculitis, myocardial infarction, cerebral ischemia, reversible airway obstruction, adult respiratory disease syndrome, chronic obstructive pulmonary disease (COPD), cryptogenic fibrosing alveolitis and bronchitis (see *J Pharmacol Exp Ther.* 2004 Feb;308(2):446-53; *Proc Natl Acad Sci U S A.* 2003 Sep 2;100(18):10529-33; *Br J Pharmacol.* 2004 Aug;142(8):1247-54).

WO02/85866 discloses sulfonylamide compounds as CB2 agonists. Especially, compounds represented by the following formula is disclosed as Example 68:



Compound A

20

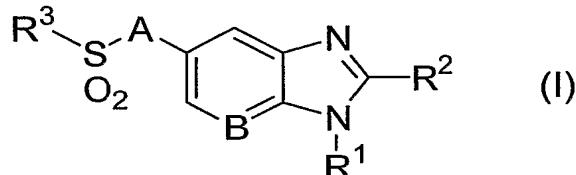
There is a need to provide new CB2 agonists that can be a good drug. In particular, preferred compounds should bind potently to the CB2 receptor whilst showing little affinity for other receptors and show functional activity as agonists. They should be well absorbed from the gastrointestinal tract, be metabolically stable and possess favorable pharmacokinetic properties. When targeted against receptors 25 in the central nervous system they should cross the blood brain barrier freely. They should be non-toxic. Furthermore, the ideal drug candidate will exist in a physical form that is stable, non-hygroscopic and easily formulated.

Summary of the Invention

30 In this invention, it has now been found out that a new class of benzimidazole compounds having an alkylsulfonyl group at the 5-position and an aliphatic group at the 2-position show CB2 agonistic activity and favorable properties as drug candidates, and thus are useful for the treatment of disease conditions mediated by CB2 activity such as inflammatory pain, nociceptive pain, neuropathic pain, fibromyalgia, chronic low back pain, visceral pain, acute cerebral ischemia, pain, chronic pain, acute pain, post herpetic neuralgia, neuropathies, neuralgia, diabetic neuropathy, HIV-related neuropathy, nerve injury, rheumatoid arthritic pain, osteoarthritic pain, back pain, cancer pain, dental pain, fibromyalgia, neuritis, sciatica, inflammation, neurodegenerative disease, cough, broncho constriction, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), colitis, cerebrovascular ischemia, emesis such as

cancer chemotherapy-induced emesis, rheumatoid arthritis, Crohn's disease, ulcerative colitis, asthma, dermatitis, seasonal allergic rhinitis, GERD, constipation, diarrhea, functional gastrointestinal disorders, irritable bowel syndrome, cutaneous T cell lymphoma, multiple sclerosis, osteoarthritis, psoriasis, systemic lupus erythematosus, diabetes, glaucoma, osteoporosis, glomerulonephritis, renal ischemia, 5 nephritis, hepatitis, cerebral stroke, vasculitis, myocardial infarction, cerebral ischemia, reversible airway obstruction, adult respiratory disease syndrome, COPD, cryptogenic fibrosing alveolitis and bronchitis (hereinafter, referred as 'CB2 Diseases').

The present invention provides a compound of the following formula (I):



10 or a pharmaceutically acceptable salt thereof, wherein:

A represents a bond or $-C(R^a)_2-$, wherein each R^a independently represents a hydrogen atom or a C_1 - C_4 alkyl group;

B represents a carbon atom or a nitrogen atom;

15 R^1 represents a C_1 - C_4 alkyl group substituted with 1 to 2 substituents independently selected from the group consisting of a C_1 - C_4 alkyl group, a hydroxy group, trifluoromethoxy, a C_1 - C_4 alkoxy group, an amino group, a C_1 - C_4 alkylamino group, a di(C_1 - C_4 alkyl)amino group, a cycloalkyl group, an alkyl-substituted cycloalkyl group, a hydroxy-substituted cycloalkyl group, a heterocyclyl group, an alkyl-substituted heterocyclyl group and a hydroxy-substituted heterocyclyl group;

20 R^2 represents a cycloalkyl group, an alkyl-substituted cycloalkyl group, a C_3 - C_{10} alkyl group, an alkoxy-substituted C_3 - C_{10} alkyl group, or a C_1 - C_2 alkyl group, said C_1 - C_2 alkyl group being substituted with 1 to 2 substituents independently selected from the group consisting of a cycloalkyl group and an alkyl-substituted cycloalkyl group; and

25 R^3 represents an aryl group, a cycloalkyl group, a heterocyclyl group or a C_1 - C_6 alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a C_1 - C_4 alkoxy group, an amino group, a C_1 - C_4 alkylamino group and a di(C_1 - C_4 alkyl)amino group.

Also, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, each as described herein, for the manufacture of a medicament for the treatment of a condition mediated by CB2 receptor activity; in particular, CB2 agonistic activity.

30 Preferably, the present invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, each as described herein, for the manufacture of a medicament for the treatment of diseases selected from CB2 Diseases.

Also, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, each as described herein, together with a 35 pharmaceutically acceptable carrier for said compound.

Also, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, each as described herein, together with a

pharmaceutically acceptable carrier for said compound and another pharmacologically active agent.

Further, the present invention provides a method of treatment of a condition mediated by CB2 receptor activity, in a mammalian subject, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, each as described herein.

Examples of conditions mediated by CB2 receptor activity include, but are not limited to, CB2 Diseases.

The compounds of the present invention may show less toxicity, good absorption, distribution, good solubility, less protein binding affinity other than CB2 receptor, less drug-drug interaction, and good metabolic stability.

Detailed Description of the Invention

In the compounds of the present invention:

Where R¹ is a substituted C₁-C₄ alkyl group, or R^a is a C₁-C₄ alkyl group, or one or more substituents of R¹ is a C₁-C₄ alkyl group, this C₁-C₄ alkyl group may be a straight or branched chain group, and examples include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and *tert*-butyl. Of these, methyl and ethyl are preferred for R¹ and R^a; isopropyl is preferred for the substituent of R¹.

Where R³ is a C₁-C₆ alkyl group, this may be a straight or branched chain group, and examples include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, *tert*-butyl, pentyl, 1-ethylpropyl and hexyl. Of these, C₁-C₄ alkyl is preferred; methyl, ethyl, isopropyl and *tert*-butyl are more preferred.

Where R² is a C₃-C₁₀ alkyl group, this may be a straight or branched chain group, and examples include, but are not limited to, propyl, isopropyl, butyl, isobutyl, sec-butyl, *tert*-butyl, pentyl, 2,2-dimethylpropyl, hexyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,2,2-trimethylpropyl, heptyl, 4,4-dimethylpentyl, 2,3,3-trimethylbutyl, octyl, 5,5-dimethylhexyl, 2,4,4-trimethylpentyl, nonyl, 6,6-dimethylheptyl, 2,5,5-trimethylhexyl, decyl, 7,7-dimethyloctyl and 2,6,6-trimethylheptyl. Of these, branched C₄-C₈ alkyl is preferred; *tert*-butyl, 2,2-dimethylpropyl, 2,2-dimethylbutyl and 2,4,4-trimethylpentyl are more preferred; *tert*-butyl and 2,2-dimethylpropyl are most preferred.

Where one or more substituents of R¹ or one or more substituents of R³ is a C₁-C₄ alkoxy group, the C₁-C₄ alky moiety of the alkoxy group may be straight or branched. Examples of such C₁-C₄ alkoxy groups include, but are not limited to, methoxy, ethoxy, propyloxy, isopropyloxy, butyloxy, isobutyloxy, sec-butyloxy and *tert*-butyloxy. Of these, methoxy is preferred.

Where one or more substituents of R¹ or one or more substituents of R³ is a C₁-C₄ alkylamino group, the C₁-C₄ alky moiety of the alkylamino group may be straight or branched. Examples of such C₁-C₄ alkylamino groups include, but are not limited to, methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, sec-butylamino and *tert*-butylamino. Of these, C₁-C₂ alkylamino is preferred; methylamino is more preferred.

Where one or more substituents of R¹ or one or more substituents of R³ is a di(C₁-C₄ alkyl)amino group, the C₁-C₄ alkyl moieties of the di(C₁-C₄ alkyl)amino group may be straight or branched.

Examples of such di(C₁-C₄ alkyl)amino groups include, but are not limited to, dimethylamino, N-methyl-N-ethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, diisobutylamino, and N,N-di(1-methylpropyl)amino. Of these, di(C₁-C₃)alkylamino is preferred; dimethylamino and diethylamino are more preferred.

Where R² is an alkoxy-substituted C₃-C₁₀ alkyl group, this alkoxy-substituted C₃-C₁₀ alkyl group represents a C₁-C₄ alkoxy-substituted C₃-C₁₀ alkyl group, and C₁-C₄ alkoxy and C₃-C₁₀ alkyl groups are as described above. Examples of an alkoxy-substituted C₃-C₁₀ alkyl group include, but are not limited to, 3-methoxypropyl, 2-methoxy-1-methylethyl, 4-methoxybutyl, 3-methoxy-2-methylpropyl, 3-ethoxy-2-methylpropyl, 5-methoxypentyl, 3-methoxy-2,2-dimethylpropyl, 3-ethoxy-2,2-dimethylpropyl, 6-methoxyhexyl, 4-methoxy-3,3-dimethylbutyl, 3-methoxy-1,2,2-trimethylpropyl, 7-methoxyheptyl, 5-methoxy-4,4-dimethylpentyl, 4-methoxy-2,3,3-trimethylbutyl, 6-methoxy-5,5-dimethylhexyl, 5-methoxy-2,4,4-trimethylpentyl, 5-ethoxy-2,4,4-trimethylpentyl, 7-methoxy-6,6-dimethylheptyl, 6-methoxy-2,5,5-trimethylhexyl, 8-methoxy-7,7-dimethyloctyl and 7-methoxy-2,6,6-trimethylheptyl. Of these, the alkoxy-substituted branched C₄-C₈ alkyl is preferred; 3-methoxy-2-methylpropyl, 3-methoxy-2,2-dimethylpropyl and 5-methoxy-2,4,4-trimethylpentyl are more preferred; 3-methoxy-2,2-dimethylpropyl is most preferred.

Where R² or R³, one or more substituents of R¹ or one or more substituents of R², is a cycloalkyl group, this represents a C₃-C₇ cycloalkyl group. Examples include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Of these, C₃-C₅ cycloalkyl is preferred; cyclopropyl is more preferred.

Where R², one or more substituents of R¹ or one or more substituents of R², is an alkyl-substituted cycloalkyl group, this alkyl-substituted cycloalkyl group represents C₁-C₄ alkyl-substituted C₃-C₇ cycloalkyl group and this C₁-C₄ alkyl group is as described above. Examples of such alkyl-substituted cycloalkyl groups include, but are not limited to, 1-methylcyclopropyl, 2-methylcyclopropyl, 2,2-dimethylcyclopropyl, 2,2,3,3-tetramethylcyclopropyl, 1-methylcyclobutyl, 1-methylcyclopentyl, 1-methylcyclohexyl and 1-methylcycloheptyl. Of these, alkyl-substituted C₃-C₅ cycloalkyl is preferred; 2,2,3,3-tetramethylcyclopropyl and 2,2-dimethylcyclopropyl are more preferred for R²; 1-methylcyclopropyl and 1-methylcyclopentyl are more preferred for R¹ and the substituent of R².

Where one or more substituents of R¹ is a hydroxy-substituted cycloalkyl group, this hydroxy-substituted cycloalkyl group represents hydroxy-substituted C₃-C₇ cycloalkyl group. Examples of a hydroxy-substituted cycloalkyl group include, but are not limited to, 1-hydroxycyclopropyl, 2-hydroxycyclopropyl, 1-hydroxycyclobutyl, 2-hydroxycyclobutyl, 3-hydroxycyclobutyl, 1-hydroxycyclopentyl, 2-hydroxycyclopentyl, 3-hydroxycyclopentyl, 1-hydroxycyclohexyl, 2-hydroxycyclohexyl, 3-hydroxycyclohexyl, 4-hydroxycyclohexyl, 1-hydroxycycloheptyl, 2-hydroxycycloheptyl, 3-hydroxycycloheptyl and 4-hydroxycycloheptyl. Of these, hydroxy-substituted C₅-C₆ cycloalkyl is preferred; 1-hydroxycyclopentyl and 1-hydroxycyclohexyl are more preferred.

Where R³ or one or more substituents of R¹ is a heterocyclyl group, this represents a 3 to 6-membered ring containing at least one hetero atom selected from N, O and S. Examples include, but are not limited to, oxiranyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 1-imidazolidinyl, 2-tetrahydrofuranyl, 1-piperidinyl, 2-piperidinyl, 1-piperazinyl, 2-tetrahydropyran, 4-tetrahydropyran, 4-morpholinyl, 4-thiomorpholinyl,

2-thienyl, 2-furyl, 2-thiazolyl, 2-oxazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrazyl and 2-pyrimidinyl. Of these, heterocycl groups containing at least one nitrogen atom are preferred; 1-pyrrolidinyl, 1-piperidinyl and 4-morpholinyl are more preferred for the substituent of R¹; 2-pyridyl, 3-pyridyl and 4-pyridyl are more preferred for R³.

5 Where one or more substituents of R¹ is an alkyl-substituted heterocycl group, this alkyl-substituted heterocycl group represents a C₁-C₄ alkyl-substituted heterocycl group and the C₁-C₄ alkyl and heterocycl moieties are as described above. Examples of an alkyl-substituted heterocycl include, but are not limited to, 2-methoxyranyl, 3-methyl-1-pyrrolidinyl, 1-methyl-2-pyrrolidinyl, 1-ethyl-2-pyrrolidinyl, 4-methyl-1-imidazolidinyl, 3-methyl-2-tetrahydrofuranyl, 2-methyl-1-piperidinyl, 10 1-methyl-2-piperidinyl, 1-ethyl-2-piperidinyl, 4-methyl-1-piperazinyl, 2-methyl-1-piperazinyl, 4-methyl-4-tetrahydropyran, 3-methyl-4-morpholinyl, 3-methyl-4-thiomorpholinyl, 3-methyl-2-thienyl, 3-methyl-2-furyl, 4-methyl-2-thiazolyl, 4-methyl-2-oxazolyl, 3-methyl-2-pyridyl, 2-methyl-3-pyridyl, 2-methyl-4-pyridyl, 3-methyl-2-pyrazyl and 4-methyl-2-pyrimidinyl. Of these, alkyl-substituted heterocycl groups containing at least one nitrogen atom are preferred; 1-methyl-2-pyrrolidinyl and 15 1-methyl-2-piperidinyl are more preferred.

Where one or more substituents of R¹ is a hydroxy-substituted heterocycl group, this heterocycl is as described above, and examples of a hydroxy-substituted heterocycl group include, but are not limited to, 3-hydroxy-1-pyrrolidinyl, 4-hydroxy-2-pyrrolidinyl, 3-hydroxy-2-tetrahydrofuran, 4-hydroxy-2-tetrahydrofuran, 3-hydroxy-3-tetrahydrofuran, 4-hydroxy-3-tetrahydrofuran, 20 3-hydroxy-2-tetrahydropyran, 4-hydroxy-2-tetrahydropyran, 5-hydroxy-2-tetrahydropyran, 3-hydroxy-3-tetrahydropyran, 4-hydroxy-3-tetrahydropyran, 5-hydroxy-3-tetrahydropyran, 3-hydroxy-4-tetrahydropyran, 4-hydroxy-4-tetrahydropyran, 3-hydroxy-2-pyrrolidinyl, 3-hydroxy-3-pyrrolidinyl, 4-hydroxy-3-pyrrolidinyl, 3-hydroxy-1-piperidinyl, 3-hydroxy-2-piperidinyl, 3-hydroxy-3-piperidinyl, 3-hydroxy-4-piperidinyl, 25 4-hydroxy-1-piperidinyl, 4-hydroxy-2-piperidinyl, 4-hydroxy-3-piperidinyl, 4-hydroxy-4-piperidinyl, 3-hydroxy-2-thienyl, 4-hydroxy-2-thienyl, 5-hydroxy-2-thienyl, 3-hydroxy-2-furyl, 4-hydroxy-2-furyl, 5-hydroxy-2-furyl, 4-hydroxy-2-thiazolyl, 5-hydroxy-2-thiazolyl, 4-hydroxy-2-oxazolyl, 5-hydroxy-2-oxazolyl, 3-hydroxy-2-pyridyl, 4-hydroxy-2-pyridyl, 5-hydroxy-2-pyridyl, 6-hydroxy-2-pyridyl, 2-hydroxy-3-pyridyl, 4-hydroxy-3-pyridyl, 5-hydroxy-3-pyridyl, 6-hydroxy-3-pyridyl, 2-hydroxy-4-pyridyl, 3-hydroxy-4-pyridyl, 30 3-hydroxy-2-pyrazyl 5-hydroxy-2-pyrazyl, 6-hydroxy-2-pyrazyl, 4-hydroxy-2-pyrimidinyl and 5-hydroxy-2-pyrimidinyl. Of these, hydroxy-substituted heterocycl groups containing at least one oxygen atom in the heterocycl group are preferred; 4-hydroxy-4-tetrahydropyran is more preferred.

Where R³ is an aryl group, this may be phenyl, naphthyl or anthracenyl. Of these, phenyl is preferred.

35 Where one or more substituents of R³ is a halogen atom, this may be a fluorine, chlorine, bromine or iodine atom. Of these, fluorine is preferred.

The term "treating" and "treatment", as used herein, refers to curative, palliative and prophylactic treatment, including reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition.

40 As used herein, the article "a" or "an" refers to both the singular and plural form of the object to

which it refers unless indicated otherwise.

Preferred classes of compounds of the present invention are those compounds of formula (I) or a pharmaceutically acceptable salt thereof, each as described herein, in which:

- (a) A is a bond;
- 5 (b) B is a carbon atom;
- (c) R¹ is a C₁-C₂ alkyl group substituted with one substituent selected from the group consisting of a C₁-C₄ alkyl group, a hydroxy group, a trifluoromethoxy group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group, a di(C₁-C₄ alkyl)amino group, a cycloalkyl group, an alkyl-substituted cycloalkyl group, a hydroxy-substituted cycloalkyl group, a heterocyclyl group, an alkyl-substituted heterocyclyl group and a hydroxy-substituted heterocyclyl group;
- 10 (d) R¹ is a C₁-C₂ alkyl group substituted with one substituent selected from the group consisting of a C₁-C₄ alkyl group, a hydroxy group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group, a di(C₁-C₄ alkyl)amino group, a cycloalkyl group, an alkyl-substituted cycloalkyl group, a heterocyclyl group and an alkyl-substituted heterocyclyl group;
- 15 (e) R¹ is a C₁-C₂ alkyl group substituted with one substituent selected from the group consisting of an isopropyl group, a methoxy group, a di(C₁-C₃)alkylamino group, a C₃-C₅ cycloalkyl group, a heterocyclyl group containing at least one nitrogen atom and an alkyl-substituted heterocyclyl group containing at least one nitrogen atom;
- (f) R¹ is a C₁-C₂ alkyl group substituted with one substituent selected from the group consisting of an isopropyl group, a trifluoromethoxy group, a dimethylamino group, a cyclopropyl group, a 1-hydroxycyclopentyl group, a 4-tetrahydropyranyl group, a 4-hydroxy-4-tetrahydropyranyl group, a 1-pyrrolidinyl group, a 1-piperidinyl group, a 4-morpholinyl group, a 1-methyl-2-pyrrolidinyl group and a 1-methyl-2-piperidinyl group;
- 20 (g) R¹ is a C₁-C₂ alkyl group substituted with one substituent selected from the group consisting of an isopropyl group, a dimethylamino group, a cyclopropyl group, a 1-pyrrolidinyl group, a 1-piperidinyl group, a 4-morpholinyl group, a 1-methyl-2-pyrrolidinyl group and a 1-methyl-2-piperidinyl group;
- (h) R² is an alkyl-substituted C₃-C₆ cycloalkyl group, a branched C₄-C₈ alkyl group, an alkoxy-substituted branched C₄-C₈ alkyl group, or a methyl group substituted with one substituent selected from the group consisting of a C₃-C₅ cycloalkyl group and an alkyl-substituted C₃-C₅ cycloalkyl group;
- 25 (i) R² is a *tert*-butyl group, a 2,2-dimethylpropyl group, a 2,2-dimethylbutyl group, a 2,4,4-trimethylpentyl group, a 3-methoxy-2,2-dimethylpropyl group, a 2,2,3,3-tetramethylcyclopropyl group, a 2,2-dimethylcyclopropyl group, a cyclopropylmethyl group, a cyclopentylmethyl group, a (1-methylcyclopropyl)methyl group or a (1-methylcyclopentyl)methyl group;
- (j) R² is a 2,2-dimethylpropyl group, a 2,2-dimethylbutyl group, a 2,4,4-trimethylpentyl group, a 3-methoxy-2,2-dimethylpropyl group, a 2,2,3,3-tetramethylcyclopropyl group, a 2,2-dimethylcyclopropyl group, a cyclopropylmethyl group, a cyclopentylmethyl group, a (1-methylcyclopropyl)methyl group or a (1-methylcyclopentyl)methyl group;
- 30 (k) R² is a *tert*-butyl group or 2,2-dimethylpropyl group;
- (l) R² is 2,2-dimethylpropyl group;
- 35 (m) R³ is a phenyl group, a C₃-C₅ cycloalkyl group, a heterocyclyl group or a C₁-C₆ alkyl group, said

phenyl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a di(C₁-C₄ alkyl)amino group;

- (n) R³ is a phenyl group, a C₃-C₅ cycloalkyl group or a C₁-C₄ alkyl group, said phenyl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a C₁-C₄ alkoxy group and a di(C₁-C₄ alkyl)amino group;
- (o) R³ is a C₁-C₄ alkyl group, hydroxy-substituted C₁-C₄ alkyl group or a trifluoromethyl group;
- (p) R³ is methyl, ethyl, isopropyl, *tert*-butyl, 3-hydroxy-2-methylprop-2-yl, 2-hydroxy-2-methylpropyl or trifluoromethyl.

Particularly preferred compounds of the present invention are those compounds of formula (I) or a pharmaceutically acceptable salt thereof in which:

- (A) A is a bond; B is a carbon atom or a nitrogen atom; R¹ is a C₁-C₄ alkyl group substituted with 1 to 2 substituents independently selected from the group consisting of a C₁-C₄ alkyl group, a hydroxy group, a trifluoromethoxy group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group, a di(C₁-C₄ alkyl)amino group, a cycloalkyl group, an alkyl-substituted cycloalkyl group, a hydroxy-substituted cycloalkyl group, a heterocyclyl group, an alkyl-substituted heterocyclyl group and a hydroxy-substituted heterocyclyl group; R² is a cycloalkyl group, an alkyl-substituted cycloalkyl group, a C₃-C₁₀ alkyl group, an alkoxy-substituted C₃-C₁₀ alkyl group, or a C₁-C₂ alkyl group substituted with 1 to 2 substituents independently selected from the group consisting of a cycloalkyl group and an alkyl-substituted cycloalkyl group; and R³ is an aryl group, a cycloalkyl group, a heterocyclyl group or a C₁-C₆ alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a di(C₁-C₄ alkyl)amino group;
- (B) A is a bond; B is a carbon atom; R¹ is a C₁-C₄ alkyl group substituted with 1 to 2 substituents independently selected from the group consisting of a C₁-C₄ alkyl group, a hydroxy group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group, a di(C₁-C₄ alkyl)amino group, a cycloalkyl group, an alkyl-substituted cycloalkyl group, a heterocyclyl group and an alkyl-substituted heterocyclyl group; R² is a cycloalkyl group, an alkyl-substituted cycloalkyl group, a C₃-C₁₀ alkyl group, an alkoxy-substituted C₃-C₁₀ alkyl group, or a C₁-C₂ alkyl group substituted with 1 to 2 substituents independently selected from the group consisting of a cycloalkyl group and an alkyl-substituted cycloalkyl group; and R³ is an aryl group, a cycloalkyl group, a heterocyclyl group or a C₁-C₆ alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a di(C₁-C₄ alkyl)amino group;
- (C) A is a bond; B is a carbon atom or a nitrogen atom; R¹ is a C₁-C₂ alkyl group substituted with one substituent selected from the group consisting of a C₁-C₄ alkyl group, a hydroxy group, a trifluoromethoxy group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group, a di(C₁-C₄ alkyl)amino group, a cycloalkyl group, an alkyl-substituted cycloalkyl group, a heterocyclyl group and an alkyl-substituted heterocyclyl group; R² is a cycloalkyl group, an alkyl-substituted cycloalkyl group, a C₃-C₁₀ alkyl group, an alkoxy-substituted C₃-C₁₀ alkyl group, or a C₁-C₂ alkyl group substituted with 1 to 2 substituents independently selected from the group consisting of a cycloalkyl group and an alkyl-substituted cycloalkyl group; and R³ is an aryl group, a cycloalkyl group, a heterocyclyl group or a C₁-C₆ alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a di(C₁-C₄ alkyl)amino group;

alkyl)amino group, a cycloalkyl group, an alkyl-substituted cycloalkyl group, a hydroxy-substituted cycloalkyl group, a heterocyclyl group, an alkyl-substituted heterocyclyl group and a hydroxy-substituted heterocyclyl group; R² is a cycloalkyl group, an alkyl-substituted cycloalkyl group, a C₃-C₁₀ alkyl group, an alkoxy-substituted C₃-C₁₀ alkyl group, or a C₁-C₂ alkyl group substituted with

5 1 to 2 substituents independently selected from the group consisting of a cycloalkyl group and an alkyl-substituted cycloalkyl group; and R³ is an aryl group, a cycloalkyl group, a heterocyclyl group or a C₁-C₆ alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a di(C₁-C₄ alkyl)amino group;

10 (D) A is a bond; B is a carbon atom; R¹ is a C₁-C₂ alkyl group substituted with one substituent selected from the group consisting of a C₁-C₄ alkyl group, a hydroxy group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group, a di(C₁-C₄ alkyl)amino group, a cycloalkyl group, an alkyl-substituted cycloalkyl group, a heterocyclyl group and an alkyl-substituted heterocyclyl group;

15 R² is a cycloalkyl group, an alkyl-substituted cycloalkyl group, a C₃-C₁₀ alkyl group, an alkoxy-substituted C₃-C₁₀ alkyl group, or a C₁-C₂ alkyl group substituted with 1 to 2 substituents independently selected from the group consisting of a cycloalkyl group and an alkyl-substituted cycloalkyl group; and R³ is an aryl group, a cycloalkyl group, a heterocyclyl group or a C₁-C₆ alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a di(C₁-C₄ alkyl)amino group;

20 (E) A is a bond; B is a carbon atom or a nitrogen atom; R¹ is a C₁-C₂ alkyl group substituted with one substituent selected from the group consisting of an isopropyl group, a methoxy group, a trifluoromethoxy group, a di(C₁-C₃)alkylamino group, a C₃-C₅ cycloalkyl group, a hydroxy-substituted C₃-C₅ cycloalkyl group, a heterocyclyl group containing at least one nitrogen or oxygen atom, an alkyl-substituted heterocyclyl group containing at least one nitrogen or oxygen atom and a hydroxy-substituted heterocyclyl group containing at least one oxygen atom; R² is a cycloalkyl group, an alkyl-substituted cycloalkyl group, a C₃-C₁₀ alkyl group, an alkoxy-substituted C₃-C₁₀ alkyl group, or a C₁-C₂ alkyl group substituted with 1 to 2 substituents independently selected from the group consisting of a cycloalkyl group and an alkyl-substituted cycloalkyl group; and R³ is an aryl group, a cycloalkyl group, a heterocyclyl group or a C₁-C₆ alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a di(C₁-C₄ alkyl)amino group;

25 (F) A is a bond; B is a carbon atom; R¹ is a C₁-C₂ alkyl group substituted with one substituent selected from the group consisting of an isopropyl group, a methoxy group, a di(C₁-C₃)alkylamino group, a C₃-C₅ cycloalkyl group, a heterocyclyl group containing at least one nitrogen atom and an alkyl-substituted heterocyclyl group containing at least one nitrogen atom; R² is a cycloalkyl group, an alkyl-substituted cycloalkyl group, a C₃-C₁₀ alkyl group, an alkoxy-substituted C₃-C₁₀ alkyl group,

30 35 (G) A is a bond; B is a carbon atom; R¹ is a C₁-C₂ alkyl group substituted with one substituent selected from the group consisting of an isopropyl group, a methoxy group, a di(C₁-C₃)alkylamino group, a C₃-C₅ cycloalkyl group, a heterocyclyl group containing at least one nitrogen atom and an alkyl-substituted heterocyclyl group containing at least one nitrogen atom; R² is a cycloalkyl group, an alkyl-substituted cycloalkyl group, a C₃-C₁₀ alkyl group, an alkoxy-substituted C₃-C₁₀ alkyl group,

40 (H) A is a bond; B is a carbon atom; R¹ is a C₁-C₂ alkyl group substituted with one substituent selected from the group consisting of an isopropyl group, a methoxy group, a di(C₁-C₃)alkylamino group, a C₃-C₅ cycloalkyl group, a heterocyclyl group containing at least one nitrogen atom and an alkyl-substituted heterocyclyl group containing at least one nitrogen atom; R² is a cycloalkyl group, an alkyl-substituted cycloalkyl group, a C₃-C₁₀ alkyl group, an alkoxy-substituted C₃-C₁₀ alkyl group,

or a C₁-C₂ alkyl group substituted with 1 to 2 substituents independently selected from the group consisting of a cycloalkyl group and an alkyl-substituted cycloalkyl group; and R³ is an aryl group, a cycloalkyl group, a heterocyclyl group or a C₁-C₆ alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a di(C₁-C₄ alkyl)amino group;

5 (G) A is a bond; B is a carbon atom or a nitrogen atom; R¹ is a C₁-C₂ alkyl group substituted with one substituent selected from the group consisting of an isopropyl group, a trifluoromethoxy group, a dimethylamino group, a cyclopropyl group, a 1-hydroxycyclopentyl group, a 4-tetrahydropyranyl

10 group, a 4-hydroxy-4-tetrahydropyranyl, a 1-pyrrolidinyl group, a 1-piperidinyl group, a 4-morpholinyl group, a 1-methyl-2-pyrrolidinyl group and a 1-methyl-2-piperidinyl group; R² is a cycloalkyl group, an alkyl-substituted cycloalkyl group, a C₃-C₁₀ alkyl group, an alkoxy-substituted C₃-C₁₀ alkyl group, or a C₁-C₂ alkyl group substituted with 1 to 2 substituents independently selected from the group consisting of a cycloalkyl group and an alkyl-substituted cycloalkyl group; and R³ is an aryl group, a cycloalkyl group, a heterocyclyl group or a C₁-C₆ alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a di(C₁-C₄ alkyl)amino group;

15 (H) A is a bond; B is a carbon atom; R¹ is a C₁-C₂ alkyl group substituted with one substituent selected from the group consisting of an isopropyl group, a dimethylamino group, a cyclopropyl group, a 1-pyrrolidinyl group, a 1-piperidinyl group, a 4-morpholinyl group, a 1-methyl-2-pyrrolidinyl group and a 1-methyl-2-piperidinyl group; R² is a cycloalkyl group, an alkyl-substituted cycloalkyl group, a C₃-C₁₀ alkyl group, an alkoxy-substituted C₃-C₁₀ alkyl group, or a C₁-C₂ alkyl group substituted with 1 to 2 substituents independently selected from the group consisting of a cycloalkyl group and an alkyl-substituted cycloalkyl group; and R³ is an aryl group, a cycloalkyl group, a heterocyclyl group or a C₁-C₆ alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a di(C₁-C₄ alkyl)amino group;

20 (I) A is a bond; B is a carbon atom or a nitrogen atom; R¹ is a C₁-C₄ alkyl group substituted with 1 to 2 substituents independently selected from the group consisting of a C₁-C₄ alkyl group, a hydroxy group, a trifluoromethoxy group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group, a di(C₁-C₄ alkyl)amino group, a cycloalkyl group, an alkyl-substituted cycloalkyl group, a hydroxy-substituted cycloalkyl group, a heterocyclyl group, an alkyl-substituted heterocyclyl group and a hydroxy-substituted heterocyclyl group; R² is an alkyl-substituted C₃-C₆ cycloalkyl group, a branched C₄-C₈ alkyl group, an alkoxy-substituted branched C₄-C₈ alkyl group, or a methyl group substituted with one substituent selected from the group consisting of a C₃-C₅ cycloalkyl group and an alkyl-substituted C₃-C₅ cycloalkyl group; and R³ is an aryl group, a cycloalkyl group, a heterocyclyl group or a C₁-C₆ alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a

hydroxy group, a phenyl group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a di(C₁-C₄ alkyl)amino group;

(J) A is a bond; B is a carbon atom; R¹ is a C₁-C₄ alkyl group substituted with 1 to 2 substituents independently selected from the group consisting of a C₁-C₄ alkyl group, a hydroxy group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group, a di(C₁-C₄ alkyl)amino group, a cycloalkyl group, an alkyl-substituted cycloalkyl group, a heterocyclyl group and an alkyl-substituted heterocyclyl group; R² is an alkyl-substituted C₃-C₆ cycloalkyl group, a branched C₄-C₈ alkyl group, an alkoxy-substituted branched C₄-C₈ alkyl group, or a methyl group substituted with one substituent selected from the group consisting of a C₃-C₅ cycloalkyl group and an alkyl-substituted C₃-C₅

cycloalkyl group; and R³ is an aryl group, a cycloalkyl group, a heterocyclyl group or a C₁-C₆ alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a di(C₁-C₄ alkyl)amino group;

(K) A is a bond; B is a carbon atom or a nitrogen atom; R¹ is a C₁-C₄ alkyl group substituted with 1 to 2 substituents independently selected from the group consisting of a C₁-C₄ alkyl group, a hydroxy group, a trifluoromethoxy group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group, a di(C₁-C₄ alkyl)amino group, a cycloalkyl group, an alkyl-substituted cycloalkyl group, a hydroxy-substituted cycloalkyl group, a heterocyclyl group, an alkyl-substituted heterocyclyl group and a hydroxy-substituted heterocyclyl group; R² is a *tert*-butyl group, a 2,2-dimethylpropyl group, a 2,2-dimethylbutyl group, a 2,4,4-trimethylpentyl group, a 3-methoxy-2,2-dimethylpropyl group, a 2,2,3,3-tetramethylcyclopropyl group, a 2,2-dimethylcyclopropyl group, a cyclopropylmethyl group, a cyclopentylmethyl group, a (1-methylcyclopropyl)methyl group and a (1-methylcyclopentyl)methyl group; and R³ is an aryl group, a cycloalkyl group, a heterocyclyl group or a C₁-C₆ alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a di(C₁-C₄ alkyl)amino group;

(L) A is a bond; B is a carbon atom; R¹ is a C₁-C₄ alkyl group substituted with 1 to 2 substituents independently selected from the group consisting of a C₁-C₄ alkyl group, a hydroxy group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group, a di(C₁-C₄ alkyl)amino group, a cycloalkyl group, an alkyl-substituted cycloalkyl group, a heterocyclyl group and an alkyl-substituted heterocyclyl group; R² is a 2,2-dimethylpropyl group, a 2,2-dimethylbutyl group, a 2,4,4-trimethylpentyl group, a 3-methoxy-2,2-dimethylpropyl group, a 2,2,3,3-tetramethylcyclopropyl group, a 2,2-dimethylcyclopropyl group, a cyclopropylmethyl group, a cyclopentylmethyl group, a (1-methylcyclopropyl)methyl group and a (1-methylcyclopentyl)methyl group; and R³ is an aryl group, a cycloalkyl group, a heterocyclyl group or a C₁-C₆ alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a di(C₁-C₄ alkyl)amino group;

- (M) A is a bond; B is a carbon atom or a nitrogen atom; R¹ is a C₁-C₄ alkyl group substituted with 1 to 2 substituents independently selected from the group consisting of a C₁-C₄ alkyl group, a hydroxy group, a trifluoromethoxy group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group, a di(C₁-C₄ alkyl)amino group, a cycloalkyl group, an alkyl-substituted cycloalkyl group, a hydroxy-substituted cycloalkyl group, a heterocyclyl group, an alkyl-substituted heterocyclyl group and a hydroxy-substituted heterocyclyl group; R² is a *tert*-butyl group or a 2,2-dimethylpropyl group; and R³ is an aryl group, a cycloalkyl group, a heterocyclyl group or a C₁-C₆ alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a di(C₁-C₄ alkyl)amino group;

(N) A is a bond; B is a carbon atom; R¹ is a C₁-C₄ alkyl group substituted with 1 to 2 substituents independently selected from the group consisting of a C₁-C₄ alkyl group, a hydroxy group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group, a di(C₁-C₄ alkyl)amino group, a cycloalkyl group, an alkyl-substituted cycloalkyl group, a heterocyclyl group and an alkyl-substituted heterocyclyl group; R² is a 2,2-dimethylpropyl group; and R³ is an aryl group, a cycloalkyl group, a heterocyclyl group or a C₁-C₆ alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a di(C₁-C₄ alkyl)amino group;

(O) A is a bond; B is a carbon atom or a nitrogen atom; R¹ is a C₁-C₂ alkyl group substituted with one substituent selected from the group consisting of a C₁-C₄ alkyl group, a hydroxy group, a trifluoromethoxy group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group, a di(C₁-C₄ alkyl)amino group, a cycloalkyl group, an alkyl-substituted cycloalkyl group, a hydroxy-substituted cycloalkyl group, a heterocyclyl group, an alkyl-substituted heterocyclyl group and a hydroxy-substituted heterocyclyl group; R² is an alkyl-substituted C₃-C₆ cycloalkyl group, a branched C₄-C₈ alkyl group, an alkoxy-substituted branched C₄-C₈ alkyl group, or a methyl group substituted with one substituent selected from the group consisting of a C₃-C₅ cycloalkyl group and an alkyl-substituted C₃-C₅ cycloalkyl group; and R³ is an aryl group, a cycloalkyl group, a heterocyclyl group or a C₁-C₆ alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a di(C₁-C₄ alkyl)amino group;

(P) A is a bond; B is a carbon atom; R¹ is a C₁-C₂ alkyl group substituted with one substituent selected from the group consisting of a C₁-C₄ alkyl group, a hydroxy group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group, a di(C₁-C₄ alkyl)amino group, a cycloalkyl group, an alkyl-substituted cycloalkyl group, a heterocyclyl group and an alkyl-substituted heterocyclyl group; R² is an alkyl-substituted C₃-C₆ cycloalkyl group, a branched C₄-C₈ alkyl group, an alkoxy-substituted branched C₄-C₈ alkyl group, or a methyl group substituted with one substituent selected from the group consisting of a C₃-C₅ cycloalkyl group and an alkyl-substituted C₃-C₅ cycloalkyl group; and R³ is an aryl group, a cycloalkyl group, a heterocyclyl group or a C₁-C₆ alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a di(C₁-C₄ alkyl)amino group;

said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a di(C₁-C₄ alkyl)amino group;

(Q) A is a bond; B is a carbon atom or a nitrogen atom; R¹ is a C₁-C₂ alkyl group substituted with one substituent selected from the group consisting of a C₁-C₄ alkyl group, a hydroxy group, a trifluoromethoxy group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group, a di(C₁-C₄ alkyl)amino group, a cycloalkyl group, an alkyl-substituted cycloalkyl group, a hydroxy-substituted cycloalkyl group, a heterocyclyl group, an alkyl-substituted heterocyclyl group and a hydroxy-substituted heterocyclyl group; R² is a *tert*-butyl group, a 2,2-dimethylpropyl group, a

2,2-dimethylbutyl group, a 2,4,4-trimethylpentyl group, a 3-methoxy-2,2-dimethylpropyl group, a 2,2,3,3-tetramethylcyclopropyl group, a 2,2-dimethylcyclopropyl group, a cyclopropylmethyl group, a cyclopentylmethyl group, a (1-methylcyclopropyl)methyl group and a (1-methylcyclopentyl)methyl group; and R³ is an aryl group, a cycloalkyl group, a heterocyclyl group or a C₁-C₆ alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a di(C₁-C₄ alkyl)amino group;

(R) A is a bond; B is a carbon atom; R¹ is a C₁-C₂ alkyl group substituted with one substituent selected from the group consisting of a C₁-C₄ alkyl group, a hydroxy group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group, a di(C₁-C₄ alkyl)amino group, a cycloalkyl group, an alkyl-substituted cycloalkyl group, a heterocyclyl group and an alkyl-substituted heterocyclyl group; R² is a 2,2-dimethylpropyl group, a 2,2-dimethylbutyl group, a 2,4,4-trimethylpentyl group, a 3-methoxy-2,2-dimethylpropyl group, a 2,2,3,3-tetramethylcyclopropyl group, a 2,2-dimethylcyclopropyl group, a cyclopropylmethyl group, a cyclopentylmethyl group, a (1-methylcyclopropyl)methyl group and a (1-methylcyclopentyl)methyl group; and R³ is an aryl group, a cycloalkyl group, a heterocyclyl group or a C₁-C₆ alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a di(C₁-C₄ alkyl)amino group;

(S) A is a bond; B is a carbon atom; R¹ is a C₁-C₂ alkyl group substituted with one substituent selected from the group consisting of an isopropyl group, a methoxy group, a di(C₁-C₃)alkylamino group, a C₃-C₅ cycloalkyl group, a heterocyclyl group containing at least one nitrogen atom and an alkyl-substituted heterocyclyl group containing at least one nitrogen; R² is an alkyl-substituted C₃-C₆ cycloalkyl group, a branched C₄-C₈ alkyl group, an alkoxy-substituted branched C₄-C₈ alkyl group, or a methyl group substituted with one substituent selected from the group consisting of a C₃-C₅ cycloalkyl group and an alkyl-substituted C₃-C₅ cycloalkyl group; and R³ is an aryl group, a cycloalkyl group, a heterocyclyl group or a C₁-C₆ alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a di(C₁-C₄ alkyl)amino group;

- (T) A is a bond; B is a carbon atom or a nitrogen atom; R¹ is a C₁-C₂ alkyl group substituted with one substituent selected from the group consisting of an isopropyl group, a methoxy group, a trifluoromethoxy group, a di(C₁-C₃)alkylamino group, a C₃-C₅ cycloalkyl group, a hydroxy-substituted C₃-C₅ cycloalkyl group, a heterocyclyl group containing at least one nitrogen or oxygen atom, an alkyl-substituted heterocyclyl group containing at least one nitrogen or oxygen atom and a hydroxy-substituted heterocyclyl group containing at least one oxygen atom; R² is a *tert*-butyl group, a 2,2-dimethylpropyl group, a 2,2-dimethylbutyl group, a 2,4,4-trimethylpentyl group, a 3-methoxy-2,2-dimethylpropyl group, a 2,2,3,3-tetramethylcyclopropyl group, a 2,2-dimethylcyclopropyl group, a cyclopropylmethyl group, a cyclopentylmethyl group, a (1-methylcyclopropyl)methyl group and a (1-methylcyclopentyl)methyl group; and R³ is an aryl group, a cycloalkyl group, a heterocyclyl group or a C₁-C₆ alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a di(C₁-C₄ alkyl)amino group;
- 5 (U) A is a bond; B is a carbon atom; R¹ is a C₁-C₂ alkyl group substituted with one substituent selected from the group consisting of an isopropyl group, a methoxy group, a di(C₁-C₃)alkylamino group, a C₃-C₅ cycloalkyl group, a heterocyclyl group containing at least one nitrogen atom and an alkyl-substituted heterocyclyl group containing at least one nitrogen atom; R² is a 2,2-dimethylpropyl group, a 2,2-dimethylbutyl group, a 2,4,4-trimethylpentyl group, a 3-methoxy-2,2-dimethylpropyl group, a 2,2,3,3-tetramethylcyclopropyl group, a 2,2-dimethylcyclopropyl group, a cyclopropylmethyl group, a cyclopentylmethyl group, a (1-methylcyclopropyl)methyl group and a (1-methylcyclopentyl)methyl group; and R³ is an aryl group, a cycloalkyl group, a heterocyclyl group or a C₁-C₆ alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a di(C₁-C₄ alkyl)amino group;
- 10 (V) A is a bond; B is a carbon atom; R¹ is a C₁-C₂ alkyl group substituted with one substituent selected from the group consisting of a C₁-C₄ alkyl group, a hydroxy group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group, a di(C₁-C₄ alkyl)amino group, a cycloalkyl group, an alkyl-substituted cycloalkyl group, a heterocyclyl group and an alkyl-substituted heterocyclyl group; R² is an alkyl-substituted C₃-C₆ cycloalkyl group, a branched C₄-C₈ alkyl group, an alkoxy-substituted branched C₄-C₈ alkyl group, or a methyl group substituted with one substituent selected from the group consisting of a C₃-C₅ cycloalkyl group and an alkyl-substituted C₃-C₅ cycloalkyl group; and R³ is a phenyl group, a C₃-C₅ cycloalkyl group or a C₁-C₄ alkyl group, said phenyl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a C₁-C₄ alkoxy group and a di(C₁-C₄ alkyl)amino group;
- 15 (W) A is a bond; B is a carbon atom or a nitrogen atom; R¹ is a C₁-C₂ alkyl group substituted with one substituent selected from the group consisting of an isopropyl group, a trifluoromethoxy group, a dimethylamino group, a cyclopropyl group, a 1-hydroxycyclopentyl group, a 4-tetrahydropyranyl
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group, a 4-hydroxy-4-tetrahydropyranyl, a 1-pyrrolidinyl group, a 1-piperidinyl group, a 4-morpholinyl group, a 1-methyl-2-pyrrolidinyl group and a 1-methyl-2-piperidinyl group; R² is a *tert*-butyl group, a 2,2-dimethylpropyl group, a 2,2-dimethylbutyl group, a 2,4,4-trimethylpentyl group, a 3-methoxy-2,2-dimethylpropyl group, a 2,2,3,3-tetramethylcyclopropyl group, a 2,2-dimethylcyclopropyl group, a cyclopropylmethyl group, a cyclopentylmethyl group, a (1-methylcyclopropyl)methyl group and a (1-methylcyclopentyl)methyl group; and R³ is methyl, ethyl, isopropyl, *tert*-butyl, 3-hydroxy-2-methylprop-2-yl, 2-hydroxy-2-methylpropyl or trifluoromethyl;

- (X) A is a bond; B is a carbon atom; R¹ is a C₁-C₂ alkyl group substituted with one substituent selected from the group consisting of an isopropyl group, a dimethylamino group, a cyclopropyl group, a

10 1-pyrrolidinyl group, a 1-piperidinyl group, a 4-morpholinyl group, a 1-methyl-2-pyrrolidinyl group and
a 1-methyl-2-piperidinyl group; R² is a 2,2-dimethylpropyl group, a 2,2-dimethylbutyl group, a
2,4,4-trimethylpentyl group, a 3-methoxy-2,2-dimethylpropyl group, a 2,2,3,3-tetramethylcyclopropyl
group, a 2,2-dimethylcyclopropyl group, a cyclopropylmethyl group, a cyclopentylmethyl group, a
(1-methylcyclopropyl)methyl group and a (1-methylcyclopentyl)methyl group; and R³ is methyl, ethyl,
15 isopropyl, *tert*-butyl, 3-hydroxy-2-methylprop-2-yl, 2-hydroxy-2-methylpropyl or trifluoromethyl;

- (Y) A is $-\text{CH}_2-$; B is a carbon atom; R¹ is a C₁-C₂ alkyl group substituted with one substituent selected from the group consisting of an isopropyl group, a methoxy group, a trifluoromethoxy group, a di(C₁-C₃)alkylamino group, a C₃-C₅ cycloalkyl group, a hydroxy-substituted C₃-C₅ cycloalkyl group, a

20 group containing at least one nitrogen or oxygen atom and a hydroxy-substituted heterocyclyl group containing at least one oxygen atom; R² is a *tert*-butyl group, a 2,2-dimethylpropyl group, a 2,2-dimethylbutyl group, a 2,4,4-trimethylpentyl group, a 3-methoxy-2,2-dimethylpropyl group, a 2,2,3,3-tetramethylcyclopropyl group, a 2,2-dimethylcyclopropyl group, a cyclopropylmethyl group, a cyclopentylmethyl group, a (1-methylcyclopropyl)methyl group and a (1-methylcyclopentyl)methyl group; and R³ is an aryl group, a cycloalkyl group, a heterocyclyl group or a C₁-C₆ alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a di(C₁-C₄ alkyl)amino group;

- 30 (Z) A is -CH₂-; B is a carbon atom; R¹ is a C₁-C₂ alkyl group substituted with one substituent selected from the group consisting of an isopropyl group, a methoxy group, a di(C₁-C₃)alkylamino group, a C₃-C₅ cycloalkyl group, a heterocyclyl group containing at least one nitrogen atom and an alkyl-substituted heterocyclyl group containing at least one nitrogen atom; R² is a 2,2-dimethylpropyl group, a 2,2-dimethylbutyl group, a 2,4,4-trimethylpentyl group, a 3-methoxy-2,2-dimethylpropyl group, a 2,2,3,3-tetramethylcyclopropyl group, a 2,2-dimethylcyclopropyl group, a cyclopropylmethyl group, a cyclopentylmethyl group, a (1-methylcyclopropyl)methyl group and a (1-methylcyclopentyl)methyl group; and R³ is an aryl group, a cycloalkyl group, a heterocyclyl group or a C₁-C₆ alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a

di(C₁-C₄ alkyl)amino group;

(AA) A is a bond; B is a nitrogen atom or a nitrogen atom; R¹ is a C₁-C₂ alkyl group substituted with one substituent selected from the group consisting of an isopropyl group, a methoxy group, a trifluoromethoxy group, a di(C₁-C₃)alkylamino group, a C₃-C₅ cycloalkyl group, a hydroxy-substituted C₃-C₅ cycloalkyl group, a heterocyclyl group containing at least one nitrogen or oxygen atom, an alkyl-substituted heterocyclyl group containing at least one nitrogen or oxygen atom and a hydroxy-substituted heterocyclyl group containing at least one oxygen atom; R² is a *tert*-butyl group, a 2,2-dimethylpropyl group, a 2,2-dimethylbutyl group, a 2,4,4-trimethylpentyl group, a 3-methoxy-2,2-dimethylpropyl group, a 2,2,3,3-tetramethylcyclopropyl group, a 2,2-dimethylcyclopropyl group, a cyclopropylmethyl group, a cyclopentylmethyl group, a (1-methylcyclopropyl)methyl group and a (1-methylcyclopentyl)methyl group; and R³ is an aryl group, a cycloalkyl group, a heterocyclyl group or a C₁-C₆ alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a di(C₁-C₄ alkyl)amino group;

(BB) A is a bond; B is a nitrogen atom; R¹ is a C₁-C₂ alkyl group substituted with one substituent selected from the group consisting of an isopropyl group, a methoxy group, a di(C₁-C₃)alkylamino group, a C₃-C₅ cycloalkyl group, a heterocyclyl group containing at least one nitrogen atom and an alkyl-substituted heterocyclyl group containing at least one nitrogen atom; R² is a 2,2-dimethylpropyl group, a 2,2-dimethylbutyl group, a 2,4,4-trimethylpentyl group, a 3-methoxy-2,2-dimethylpropyl group, a 2,2,3,3-tetramethylcyclopropyl group, a 2,2-dimethylcyclopropyl group, a cyclopropylmethyl group, a cyclopentylmethyl group, a (1-methylcyclopropyl)methyl group and a (1-methylcyclopentyl)methyl group; and R³ is an aryl group, a cycloalkyl group, a heterocyclyl group or a C₁-C₆ alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a C₁-C₄ alkoxy group, an amino group, a C₁-C₄ alkylamino group and a di(C₁-C₄ alkyl)amino group;

One embodiment of the invention provides a compound selected from the group consisting of:

- 30 1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-(isopropylsulfonyl)-1*H*-benzimidazole;
- 1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-(ethylsulfonyl)-1*H*-benzimidazole;
- 1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-[(trifluoromethyl)sulfonyl]-1*H*-benzimidazole;
- 1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-(methylsulfonyl)-1*H*-benzimidazole;
- 2-(2,2-dimethylpropyl)-5-(isopropylsulfonyl)-1-(2-pyrrolidin-1-ylethyl)-1*H*-benzimidazole;
- 35 2-[2-(2,2-dimethylpropyl)-5-(isopropylsulfonyl)-1*H*-benzimidazol-1-yl]-N,N-dimethylethanamine; and
- 1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-(phenylsulfonyl)-1*H*-benzimidazole;
- or a pharmaceutically acceptable salt thereof.

One embodiment of the invention provides a compound selected from the group consisting of:

- 40 2-*tert*-butyl-1-(cyclopropylmethyl)-5-(isopropylsulfonyl)-1*H*-benzimidazole;

- 2-(2,2-dimethylpropyl)-5-(ethylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazole;
 2-(2,2-dimethylpropyl)-5-(ethylsulfonyl)-1-(tetrahydrofuran-2-ylmethyl)-1*H*-benzimidazole;
 4-[[2-(2,2-dimethylpropyl)-5-(isopropylsulfonyl)-1*H*-benzimidazol-1-yl]methyl]tetrahydro-2*H*-pyran-4-ol;
 1-[[2-(2,2-dimethylpropyl)-5-(ethylsulfonyl)-1*H*-benzimidazol-1-yl]methyl]cyclopentanol;
- 5 2-(2,2-dimethylpropyl)-6-(ethylsulfonyl)-3-(tetrahydro-2*H*-pyran-4-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine;
 4-[[2-(2,2-dimethylpropyl)-6-(isopropylsulfonyl)-3*H*-imidazo[4,5-*b*]pyridin-3-yl]methyl]tetrahydro-2*H*-pyran-4-ol;
 2-[2-(2,2-dimethylpropyl)-6-(isopropylsulfonyl)-3*H*-imidazo[4,5-*b*]pyridin-3-yl]-*N,N*-dimethylethanamine;
 2-[2-(2,2-dimethylpropyl)-6-(isopropylsulfonyl)-3-(tetrahydro-2*H*-pyran-4-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridi
 10 ne;
- 2-*tert*-butyl-5-[(isopropylsulfonyl)methyl]-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazole;
 2-*tert*-butyl-5-(ethylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazole;
 1-[[2-*tert*-butyl-5-(isopropylsulfonyl)-1*H*-benzimidazol-1-yl]methyl]cyclopentanol; and
 2-(2,2-dimethylpropyl)-5-(ethylsulfonyl)-1-[2-(trifluoromethoxy)ethyl]-1*H*-benzimidazole;
- 15 or a pharmaceutically acceptable salt thereof.

One embodiment of the invention provides a compound selected from the group consisting of:

- 2-[[1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazol-5-yl]sulfonyl]-2-methylpropan-1-ol;
 1-[[1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazol-5-yl]sulfonyl]-2-methylpropan-2-ol;
- 20 2-[[2-*tert*-butyl-1-(cyclopropylmethyl)-1*H*-benzimidazol-5-yl]sulfonyl]-2-methylpropan-1-ol;
 1-[[2-*tert*-butyl-1-(cyclopropylmethyl)-1*H*-benzimidazol-5-yl]sulfonyl]-2-methylpropan-2-ol;
 1-((2-*tert*-butyl-5-[(2-hydroxy-1,1-dimethylethyl)sulfonyl]-1*H*-benzimidazol-1-yl)methyl)cyclopentanol;
 2-((2-(2,2-dimethylpropyl)-1-[2-(trifluoromethoxy)ethyl]-1*H*-benzimidazol-5-yl)sulfonyl)-2-methylpropan-1-o
 l;
- 25 1-[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]sulfonyl]-2-methylpropan-2-ol;
 2-*tert*-butyl-6-(ethylsulfonyl)-3-(tetrahydro-2*H*-pyran-4-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine;
 2-*tert*-butyl-6-(isopropylsulfonyl)-3-(tetrahydro-2*H*-pyran-4-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine;
 2-(2,2-dimethylpropyl)-6-(ethylsulfonyl)-3-[2-(trifluoromethoxy)ethyl]-3*H*-imidazo[4,5-*b*]pyridine;
 2-(2,2-dimethylpropyl)-6-(isopropylsulfonyl)-3-[2-(trifluoromethoxy)ethyl]-3*H*-imidazo[4,5-*b*]pyridine
 30 4-[[2-*tert*-butyl-5-(*tert*-butylsulfonyl)-1*H*-benzimidazol-1-yl]methyl]tetrahydro-2*H*-pyran-4-ol; and
 2-*tert*-butyl-5-(ethylsulfonyl)-1-(tetrahydro-2*H*-pyran-2-ylmethyl)-1*H*-benzimidazole;
 or a pharmaceutically acceptable salt thereof.

35 Pharmaceutically acceptable salts of a compound of formula (I) include the acid addition (including disalts) thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulfate, naphthylate, 2-napsylate,

nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002). A pharmaceutically acceptable salt of a compound of formula (I) may be readily prepared by mixing together solutions of the compound of formula (I) and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionization in the salt may vary from completely ionized to almost non-ionized.

The compounds of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising a compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

Pharmaceutically acceptable solvates in accordance with the invention include hydrates and solvates wherein the solvent of crystallization may be isotopically substituted, e.g. D₂O, d₆-acetone, d₆-DMSO.

Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionized, partially ionized, or non-ionized. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Halebian (August 1975).

Hereinafter all references to a compound of formula (I) include references to salts and complexes thereof and to solvates and complexes of salts thereof.

The term "compound of the invention" or "compounds of the invention" refers to, unless indicated otherwise, a compound of formula (I) as hereinbefore defined, polymorphs, prodrugs, and isomers thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labeled compounds of formula (I).

Also within the scope of the invention are so-called 'prodrugs' of the compounds of formula (I). Thus certain derivatives of compounds of formula (I) which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of formula (I) having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in 'Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T Higuchi and W Stella)' and 'Bioreversible Carriers in Drug Design', Pergamon Press, 1987 (ed. E B Roche, American Pharmaceutical Association).

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of formula (I) with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in "Design of Prodrugs" by H Bundgaard (Elsevier, 1985). Some examples of prodrugs in accordance with the invention include:

(i) where the compound of formula (I) contains an alcohol functionality (-OH), an ether thereof, for example, replacement of the hydrogen with (C₁-C₆)alkanoyloxymethyl; and

(ii) where the compound of formula (I) contains a primary or secondary amino functionality (-NH₂ or -NHR where R ≠ H), an amide thereof, for example, replacement of one or both hydrogens with (C₁-C₁₀)alkanoyl.

Further examples of replacement groups in accordance with the foregoing examples and examples 5 of other prodrug types may be found in the aforementioned references.

Finally, certain compounds of formula (I) may themselves act as prodrugs of other compounds of formula (I).

Compounds of formula (I) containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where the compound contains, for example, a keto or oxime group or an aromatic 10 moiety, tautomeric isomerism ('tautomerism') can occur. It follows that a single compound may exhibit more than one type of isomerism.

Included within the scope of the present invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of formula (I), including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition salts wherein the 15 counterion is optically active, for example, D-lactate or L-lysine, or racemic, for example, DL-tartrate or DL-arginine.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

20 Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula (I) contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled 25 person.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% isopropanol, typically from 2 to 20%, and from 0 to 5% of an alkylamine, typically 0.1% diethylamine.

30 Concentration of the eluate affords the enriched mixture.

Stereoisomeric conglomerates may be separated by conventional techniques known to those skilled in the art - see, for example, "Stereochemistry of Organic Compounds" by E L Eliel (Wiley, New York, 1994).

The present invention includes all pharmaceutically acceptable isotopically-labeled compounds of 35 formula (I) wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ²H and ³H, carbon, such as ¹¹C, ¹³C and ¹⁴C, chlorine, such as ³⁶Cl, fluorine, such as ¹⁸F, iodine, such as ¹²³I and ¹²⁵I, nitrogen, such as ¹³N and ¹⁵N, oxygen, such as ¹⁵O, ¹⁷O and ¹⁸O, 40 phosphorus, such as ³²P, and sulfur, such as ³⁵S.

Certain isotopically-labeled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^3H , and carbon-14, i.e. ^{14}C , are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

5 Substitution with heavier isotopes such as deuterium, i.e. ^2H , may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

10 Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

All of the compounds of the formula (I) can be prepared by the procedures described in the general
15 methods presented below or by the specific methods described in the Examples section and the Preparations section, or by routine modifications thereof. The present invention also encompasses any one or more of these processes for preparing the compounds of formula (I), in addition to any novel intermediates used therein.

20 **General Synthesis**

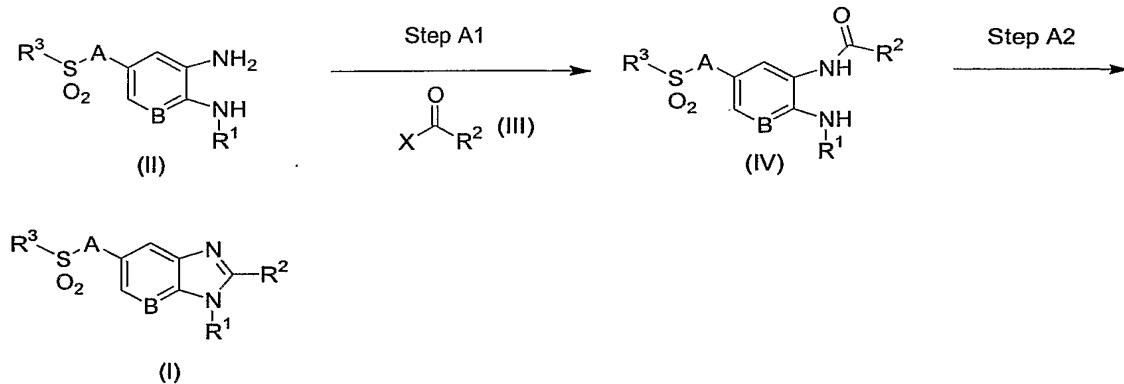
The compounds of the present invention may be prepared by a variety of processes well known for the preparation of compounds of this type, for example as shown in the following Methods A to E.

The following Methods A and B illustrate the preparation of compounds of formula (I). Methods C through E illustrate the preparation of various intermediates.

25 Unless otherwise indicated, R^1 , R^2 , R^3 , A and B in the following Methods are as defined above. The term "protecting group", as used hereinafter, means a hydroxy, carboxy or amino-protecting group. Typical hydroxy, carboxy or amino-protecting groups are described in Protective Groups in Organic Synthesis edited by T. W. Greene *et al.* (John Wiley & Sons, 1999). All starting materials in the following general syntheses may be commercially available or obtained by conventional methods known to those
30 skilled in the art, such as Journal of Organic Chemistry, 48(4), 604-5; 1983, Canadian Journal of Chemistry, 62(8), 1544-7; 1984, Chemical & Environmental Research, 11(1 & 2), 63-75; 2002, and Chemical & Pharmaceutical Bulletin, 38(10), 2853-8; 1990, the disclosures of which are incorporated herein by reference.

35 **Method A**

This illustrates the preparation of compounds of formula (I).

Reaction Scheme A

In Reaction Scheme A, X is a hydroxy group or a leaving group.

The term "leaving group", as used herein, signifies a group capable of being substituted by nucleophilic groups, such as a hydroxy group, amines or carboanions and examples of such leaving groups include halogen atoms, an alkylsulfonyl group and an arylsulfonyl group. Of these, a chlorine atom, a methylsulfonyl group, a trifluoromethylsulfonyl group and 4-methylphenylsulfonyl group are preferred.

Step A1

In this step, the compound of formula (IV) is prepared by (A1a) nucleophilic substitution or (A1b) condensing reaction of the compound of formula (II), which may be prepared by the following method C or D, with the compound of formula (III), which is commercially available or obtained by conventional methods known to those skilled in the art.

(A1a) nucleophilic substitution

The reaction is normally and preferably effected in the presence of solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve reagents, at least to some extent. Examples of suitable solvents include: amides, such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide and hexamethylphosphoric triamide; nitriles, such as acetonitrile and benzonitrile; and esters, such as ethyl acetate and methyl acetate. Of these solvents, esters are preferred; ethyl acetate is more preferred.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting materials. However, in general, it is convenient to carry out the reaction at a temperature of from about -78°C to about 120°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the starting materials and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from about 5 minutes to about 24 hours will usually suffice.

(A1b) condensing reaction

The reaction is normally and preferably effected in the presence of solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve reagents, at least to some extent. Examples

of suitable solvents include: aliphatic hydrocarbons, such as hexane, heptane and petroleum ether; halogenated hydrocarbons, such as dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane; aromatic hydrocarbons, such as benzene, toluene and nitrobenzene; amides, such as formamide, 5 N,N-dimethylformamide and N,N-dimethylacetamide; ethers, such as diethyl ether diisopropyl ether and tetrahydrofuran; and nitriles, such as acetonitrile and benzonitrile. Of these solvents, ethers are preferred; tetrahydrofuran is more preferred.

The reaction is carried out in the presence of a condensing agent. There is likewise no particular restriction on the nature of the condensing agents used, and any condensing agent commonly used in reactions of this type may equally be used here. Examples of such condensing agents include: azodicarboxylic acid di-lower alkyl ester-triphenylphosphines, such as diethyl azodicarboxylate-triphenylphosphine; 2-halo-1-lower alkyl pyridinium halides, such as 2-chloro-1-methyl pyridinium iodide; diarylphosphorylazides, such as diphenylphosphorylazide (DPPA); chloroformates, such as ethyl chloroformate and isobutyl chloroformate; phosphoryl chlorides, such as diethyl phosphoryl chloride; phosphorocyanides, such as diethyl phosphorocyanide (DEPC); imidazole derivatives, such as *N,N'*- carbonyldiimidazole (CDI); carbodiimide derivatives, such as *N,N'*-dicyclohexylcarbodiimide (DCC) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDAPC); and sulfonyl chloride derivatives, such as 2,4,6-triisopropylbenzenesulfonyl chloride.

Of these, EDAPC is preferred.

20 Reagents, such as N-hydroxysuccinimide (HONSu), 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benztriazine (HOObt) and N-hydroxybenztriazole (HObt), may be employed for this step. Of these, HObt is preferred.

The reaction may be carried out in the presence of base. There is likewise no particular restriction on the nature of the bases used, and any base commonly used in reactions of this type may 25 equally be used here. Examples of such bases include: amines, such as *N*-methylmorpholine, triethylamine, tripropylamine, tributylamine, diisopropylethylamine, dicyclohexylamine, *N*-methylpiperidine, pyridine, 4-pyrrolidinopyridine, picoline, 4-(*N,N*-dimethylamino)pyridine, 2,6-di(*t*-butyl)-4-methylpyridine, quinoline, *N,N*-dimethylaniline, *N,N*-diethylaniline, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Of these, 30 *N*-methylmorpholine is preferred.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting materials. However, in general, it is convenient to carry out the reaction at a temperature of from about -78°C to about 120°C. The time required for the 35 reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the starting materials and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from about 5 minutes to about 24 hours will usually suffice.

In this step, the desired compound of formula (I) is prepared by the annealing of the compound of formula (IV) prepared as described in Step A1.

The reaction is normally and preferably effected in the presence of solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve reagents, at least to some extent. Examples of suitable solvents include: amides, such as formamide, *N,N*-dimethylformamide, *N,N*-dimethylacetamide and hexamethylphosphoric triamide; alcohols, such as methanol, ethanol, propanol, 2-propanol and butanol; nitriles, such as acetonitrile and benzonitrile; and esters, such as ethyl acetate and methyl acetate. Of these solvents, alcohols and esters are preferred; ethanol and ethyl acetate are more preferred.

The reaction is carried out in the presence of an acid or base. There is likewise no particular restriction on the nature of the acids or bases used, and any ones commonly used in reactions of this type may equally be used here. Examples of such acids or bases include: acids, such as hydrochloric acid, sulfuric acid, or p-toluenesulfonic acid; and alkali metal hydroxides, such as lithium hydroxide, sodium hydroxide and potassium hydroxide. Of these, p-toluenesulfonic acid and sodium hydroxide are preferred.

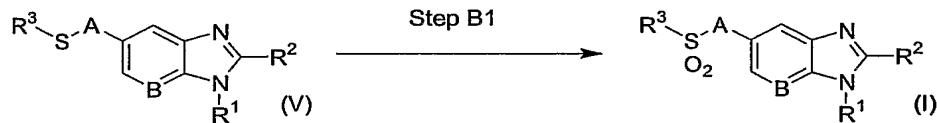
The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting materials. However, in general, it is convenient to carry out the reaction at a temperature of from about 0°C to about 120°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the starting materials and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from about 5 minutes to about 24 hours will usually suffice.

In this reaction, microwave can be employed to accelerate the reaction. In the case of employing microwave, the reaction at a temperature may be from about 0°C to about 130°C and the reaction time from about 5 minutes to about 12 hours will usually suffice.

Method B

This illustrates the preparation of compounds of formula (I).

Reaction Scheme B



Step B1

In this step, the desired compound of formula (I) is prepared by oxidation of the compound of formula (V), which may be prepared by the following method E.

The reaction is normally and preferably effected in the presence of solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve reagents, at least to some extent. Examples

of suitable solvents include: aliphatic hydrocarbons, such as hexane, heptane and petroleum ether; halogenated hydrocarbons, such as dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane; and aromatic hydrocarbons, such as benzene, toluene and nitrobenzene. Of these solvents, halogenated hydrocarbons are preferred; dichloromethane is more preferred.

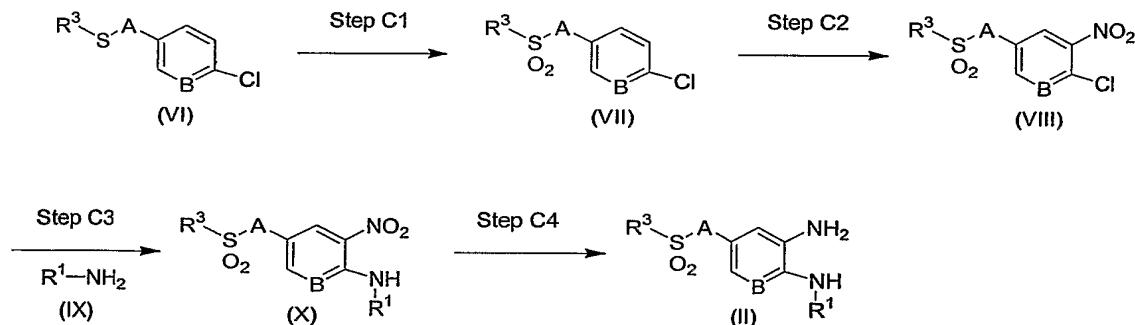
5 The reaction is carried out in the presence of an oxidizing agent. There is likewise no particular restriction on the nature of the oxidizing agents used, and any oxidizing agent commonly used in reactions of this type may equally be used here. Examples of such oxidizing agents include: high valence iodine oxidizing agents, such as NaIO₄ or 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one(Dess-Martin periodinane); or peracids, such as H₂O₂, CH₃COOOH or 10 m-chloroperbenzoic acid(mCPBA). Of these, mCPBA is preferred.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting materials. However, in general, it is convenient to carry out the reaction at a temperature of from about -78°C to about 120°C. The time required for the 15 reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the starting materials and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from about 5 minutes to about 24 hours will usually suffice.

20 Method C

This illustrates the preparation of compounds of formula (II).

Reaction Scheme C



Step C1

In this step, the compound of formula (VII) is prepared by oxidation of the compound of formula 25 (VI), which is commercially available or obtained by conventional methods known to those skilled in the art. The reaction may be carried out under the same conditions as described in Step B1.

Step C2

In this step, the compound of formula (VIII) is prepared by nitration of the compound of formula (VII) prepared as described in Step C1.

30 The reaction is normally and preferably effected in the mixture of concentrated nitric acid and concentrated sulfuric acid or the mixture of potassium nitrate and sulfuric acid.

The reaction can take place over a wide range of temperatures, and the precise reaction

temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting materials. However, in general, it is convenient to carry out the reaction at a temperature of from about -78°C to about 120°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the 5 nature of the starting materials and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from about 5 minutes to about 24 hours will usually suffice.

Step C3

In this step, the compound of formula (X) is prepared by reaction of the compound of formula 10 (VIII) prepared as described in Step C2 with the compound of formula (IX), which is commercially available or obtained by conventional methods known to those skilled in the art.

The reaction is normally and preferably effected in the presence of solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve reagents, at least to some extent. Examples 15 of suitable solvents include: amides, such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide and hexamethylphosphoric triamide; alcohols, such as methanol, ethanol, propanol, 2-propanol and butanol; nitriles, such as acetonitrile and benzonitrile; and sulfoxides, such as dimethyl sulfoxide and sulfolane. Of these solvents, alcohols are preferred; ethanol is more preferred.

The reaction can take place over a wide range of temperatures, and the precise reaction 20 temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting materials. However, in general, it is convenient to carry out the reaction at a temperature of from about -78°C to about 120°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the starting materials and solvent employed. However, provided that the reaction is effected 25 under the preferred conditions outlined above, a period of from about 5 minutes to about 24 hours will usually suffice.

In this reaction, microwave can be employed to accelerate the reaction. In the case of employing microwave, the reaction at a temperature may be from about 0°C to about 130°C and the reaction time from about 5 minutes to about 12 hours will usually suffice.

30

Step C4

In this step, the compound of formula (II) is prepared by reduction of the nitro group of the compound of formula (X) prepared as described in Step C3.

The reaction is normally and preferably effected in the presence of solvent. There is no 35 particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve reagents, at least to some extent. Examples of suitable solvents include: aromatic hydrocarbons, such as benzene and toluene; alcohols, such as methanol, ethanol, propanol, 2-propanol and butanol; and esters, such as ethyl acetate. Of these solvents, methanol, ethanol and the mixture of methanol and ethyl acetate are preferred.

40 The reaction is carried out in the presence of a reducing agent. There is likewise no particular

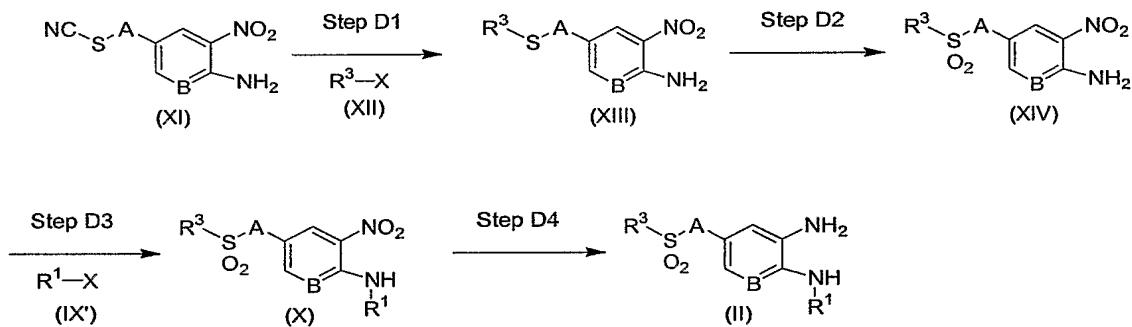
restriction on the nature of the reducing agents used, and any reducing agent commonly used in reactions of this type may equally be used here. Examples of such reducing agents include: combinations of hydrogen gas and a catalyst such as palladium-carbon, platinum and Raney nickel; and a combination of zinc and hydrochloric acid. Of these, palladium-carbon is preferred. In the case of 5 employing palladium-carbon, the pressure of hydrogen gas preferably range from about 1 atom to about 4 atom.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting materials. However, in general, it is convenient to 10 carry out the reaction at a temperature of from about -78°C to about 120°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the starting materials and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from about 5 minutes to about 24 hours will usually suffice.

15 Method D

This illustrates the preparation of compounds of formula (II).

Reaction Scheme D



In Reaction Scheme D, X is as defined above.

Step D1

20 In this step, the compound of formula (XIII) is prepared by reaction of the compound of formula (XI), which is commercially available or obtained by conventional methods known to those skilled in the art, with the compound of formula (XII), which is commercially available.

The reaction is normally and preferably effected in the presence of solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on 25 the reaction or the reagents involved and that it can dissolve reagents, at least to some extent. Examples of suitable solvents include: halogenated hydrocarbons, such as dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane; amides, such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide and hexamethylphosphoric triamide; nitriles, such as acetonitrile and benzonitrile; sulfoxides, such as dimethyl 30 sulfoxide and sulfolane; and alcohols, such as methanol, ethanol and isopropanol. Of these an alcohol is preferred.

The reaction is carried out in the presence of a base. There is likewise no particular restriction

on the nature of the bases used, and any base commonly used in reactions of this type may equally be used here. Examples of such bases include: alkali metal alkoxides, such as sodium methoxide, sodium ethoxide and potassium t-butoxide; alkali metal hydroxide such as potassium hydroxide and sodium hydroxide; and amines, such as *N*-methylmorpholine, triethylamine, tripropylamine, tributylamine, diisopropylethylamine, dicyclohexylamine, *N*-methylpiperidine, pyridine, 4-pyrrolidinopyridine, picoline, 4-(*N,N*-dimethylamino)pyridine, 2,6-di(*t*-butyl)-4-methylpyridine, quinoline, *N,N*-dimethylaniline, *N,N*-diethylaniline, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Of these, alkali metal hydroxides are preferred; potassium hydroxide is more preferred.

- 10 The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting materials. However, in general, it is convenient to carry out the reaction at a temperature of from about -78°C to about 120°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the
- 15 nature of the starting materials and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from about 5 minutes to about 24 hours will usually suffice.

The following Steps D2 and D3 are interchangeable. Thus, depending on the nature of the compound, oxidation of sulfide may be employed after the reaction with the compound of the formula (IX).

20 **Step D2**

In this step, the compound of formula (XIV) is prepared by oxidation of the compound of formula (XIII) prepared as described in Step D1. The reaction may be carried out under the same conditions as described in Step B1.

Step D3

- 25 In this step, the compound of formula (X) is prepared by reaction of the compound of formula (XIV) prepared as described in Step D2 with the compound of formula (IX'), which is commercially available.

The reaction is normally and preferably effected in the presence of solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on

30 the reaction or the reagents involved and that it can dissolve reagents, at least to some extent. Examples of suitable solvents include: amides, such as formamide, *N,N*-dimethylformamide, *N,N*-dimethylacetamide and hexamethylphosphoric triamide; alcohols, such as methanol, ethanol, propanol, 2-propanol and butanol; nitriles, such as acetonitrile and benzonitrile; and sulfoxides, such as dimethyl sulfoxide and sulfolane. Of these solvents, amides are preferred; *N,N*-dimethylformamide is more preferred.

- 35 The reaction is carried out in the presence of a base. There is likewise no particular restriction on the nature of the bases used, and any base commonly used in reactions of this type may equally be used here. Examples of such bases include: alkali metal hydrides, such as lithium hydride, sodium hydride and potassium hydride; alkali metal alkoxides, such as sodium methoxide, sodium ethoxide and potassium t-butoxide; alkali metal alkoxides, such as sodium methoxide, sodium ethoxide and potassium t-butoxide; alkali metal hydroxide such as potassium hydroxide and sodium hydroxide; and amines, such

as *N*-methylmorpholine, triethylamine, tripropylamine, tributylamine, diisopropylethylamine, dicyclohexylamine, *N*-methylpiperidine, pyridine, 4-pyrrolidinopyridine, picoline, 4-(*N,N*-dimethylamino)pyridine, 2,6-di(*t*-butyl)-4-methylpyridine, quinoline, *N,N*-dimethylaniline, *N,N*-diethylaniline, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO) and 5 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Of these, alkali metal hydrides are preferred; sodium hydride is more preferred.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting materials. However, in general, it is convenient to 10 carry out the reaction at a temperature of from about -78°C to about 120°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the starting materials and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from about 5 minutes to about 24 hours will usually suffice.

15

Step D4

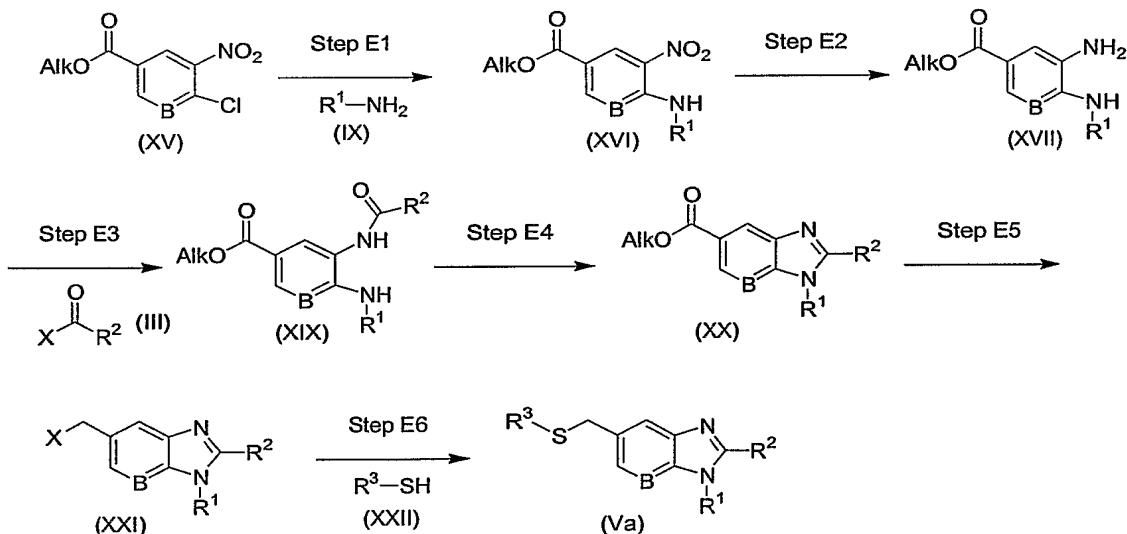
In this step, the compound of formula (II) is prepared by reduction of the compound of formula (X) prepared as described in Step D3. The reaction may be carried out under the same conditions as described in Step C4.

20

Method E

This illustrates the preparation of compounds of formula (V) wherein A is -CH₂-.

Reaction Scheme E



In Reaction Scheme E, Alk is a C₁-C₄ alkyl group, preferably methyl, and X is as defined above.

25

Step E1 and E2

In this step, the compound of formula (XVII) is prepared by reaction of the compound of formula (XV), which is commercially available or obtained by conventional methods known to those skilled in the art, with the compound of formula (IX), which is commercially available and the reduction of the resulting

compound. The reaction may be carried out under the same conditions as described in Steps C3 and C4.

Step E3 and E4

In this step, the compound of formula (XX) is prepared by reaction of the compound of formula (XVII) prepared as described in Step E2 with the compound of formula (III), which is commercially available and the annealing of the resulting compound. The reaction may be carried out under the same conditions as described in Steps A1 and A2.

Step E5

In this step, the compound of formula (XXI) is prepared by (E5a) reduction of the compound of formula (XX) prepared as described in Step E4 and (E5b) nucleophilic substitution of the resulting compound.

(E5a) reduction

The reaction is normally and preferably effected in the presence of solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve reagents, at least to some extent. Examples of suitable solvents include: aliphatic hydrocarbons, such as hexane, heptane and petroleum ether; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane; and aromatic hydrocarbons, such as benzene, toluene and nitrobenzene. Of these solvents, tetrahydrofuran is preferred.

The reaction is carried out in the presence of a reducing agent. There is likewise no particular restriction on the nature of the reducing agents used, and any reducing agent commonly used in reactions of this type may equally be used here. Examples of such reducing agents include: borane reagents, such as boran-tetrahydrofuran complex, boran-dimethyl sulfide complex (BMS) and 9-borabicyclo[3.3.1]nonane (9-BBN); and hydride compounds such as lithium aluminum hydride and diisobutyl aluminum hydride. Of these, lithium aluminum hydride is preferred.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting materials. However, in general, it is convenient to carry out the reaction at a temperature of from about -78°C to about 120°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the starting materials and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from about 5 minutes to about 24 hours will usually suffice.

(E5b) nucleophilic substitution

The reaction is carried out in the presence of the reagent. There is likewise no particular restriction on the nature of the reagents used, and any reagent commonly used in reactions of this type may equally be used here. Examples of such reagents include: methanesulfonyl chloride (MsCl), trifluoromethanesulfonyl chloride and toluensulfonyl chloride(TsCl). Of these, MsCl is preferred.

The reaction is normally and preferably effected in the presence of solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve reagents, at least to some extent. Examples of suitable solvents include: halogenated hydrocarbons, such as dichloromethane, chloroform, carbon

tetrachloride and 1,2-dichloroethane; and ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane. Of these solvents, dichloromethane is preferred.

The reaction is carried out in the presence of a base. There is likewise no particular restriction on the nature of the bases used, and any base commonly used in reactions of this type may equally be used here. Examples of such bases include: amines, such as *N*-methylmorpholine, triethylamine, tripropylamine, tributylamine, diisopropylethylamine, dicyclohexylamine, *N*-methylpiperidine, pyridine, 4-pyrrolidinopyridine, picoline, 4-(*N,N*-dimethylamino)pyridine, 2,6-di(*t*-butyl)-4-methylpyridine, quinoline, *N,N*-dimethylaniline, *N,N*-diethylaniline, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Of these, triethylamine is preferred.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting materials. However, in general, it is convenient to carry out the reaction at a temperature of from about -78°C to about 120°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the starting materials and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from about 5 minutes to about 24 hours will usually suffice.

Step E6

In this step, the compound of formula (Va) is prepared by reaction of the compound of formula (XXI) prepared as described in Step E5 with the compound of formula (XXII), which is commercially available.

The reaction is normally and preferably effected in the presence of solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve reagents, at least to some extent. Examples of suitable solvents include: amides, such as formamide, *N,N*-dimethylformamide, *N,N*-dimethylacetamide and hexamethylphosphoric triamide; alcohols, such as methanol, ethanol, propanol, 2-propanol and butanol; nitriles, such as acetonitrile and benzonitrile; and sulfoxides, such as dimethyl sulfoxide and sulfolane. Of these solvents, amides are preferred; *N,N*-dimethylformamide is more preferred.

The reaction is carried out in the presence of a base. There is likewise no particular restriction on the nature of the bases used, and any base commonly used in reactions of this type may equally be used here. Examples of such bases include: alkali metal hydrides, such as lithium hydride, sodium hydride and potassium hydride; alkali metal alkoxides, such as sodium methoxide, sodium ethoxide and potassium *t*-butoxide; alkali metal alkoxides, such as sodium methoxide, sodium ethoxide and potassium *t*-butoxide; alkali metal hydroxide such as potassium hydroxide and sodium hydroxide; and amines, such as *N*-methylmorpholine, triethylamine, tripropylamine, tributylamine, diisopropylethylamine, dicyclohexylamine, *N*-methylpiperidine, pyridine, 4-pyrrolidinopyridine, picoline, 4-(*N,N*-dimethylamino)pyridine, 2,6-di(*t*-butyl)-4-methylpyridine, quinoline, *N,N*-dimethylaniline, *N,N*-diethylaniline, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Of these, alkali metal hydrides are preferred; sodium hydride

is more preferred.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting materials. However, in general, it is convenient to 5 carry out the reaction at a temperature of from about -78°C to about 120°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the starting materials and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from about 5 minutes to about 24 hours will usually suffice.

10

The compounds of formula (I), and the intermediates above-mentioned preparation methods can be isolated and purified by conventional procedures, such as distillation, recrystallization or chromatographic purification.

Compounds of the invention intended for pharmaceutical use may be administered as crystalline 15 or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

They may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof). Generally, they 20 will be administered as a pharmaceutical composition or formulation in association with one or more pharmaceutically acceptable carriers or excipients. The term "carrier" or "excipient" is used herein to describe any ingredient other than the compound(s) of the invention. The choice of carrier or excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

25 Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in 'Remington's Pharmaceutical Sciences', 19th Edition (Mack Publishing Company, 1995).

30 ORAL ADMINISTRATION

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid formulations such as, for example, 35 tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films (including muco-adhesive), ovules, sprays and liquid formulations.

Liquid formulations include, for example, suspensions, solutions, syrups and elixirs. Such 40 formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one

or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986 by Liang and Chen (2001).

For tablet dosage forms, depending on dose, the drug may make up from about 1 wt% to about 80 wt% of the dosage form, more typically from about 5 wt% to about 60 wt% of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinized starch and sodium alginate. Generally, the disintegrant will comprise from about 1 wt% to about 25 wt%, preferably from about 5 wt% to about 20 wt% of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinized starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from about 0.2 wt% to about 5 wt% of the tablet, and glidants may comprise from about 0.2 wt% to about 1 wt% of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from about 0.25 wt% to about 10 wt%, preferably from about 0.5 wt% to about 3 wt% of the tablet.

Other possible ingredients include anti-oxidants, colorants, flavoring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 wt% to about 90 wt% binder, from about 0 wt% to about 85 wt% diluent, from about 2 wt% to about 10 wt% disintegrant, and from about 0.25 wt% to about 10 wt% lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tableting.

The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated.

The formulation of tablets is discussed in "Pharmaceutical Dosage Forms: Tablets, Vol. 1", by H. Lieberman and L. Lachman, Marcel Dekker, N.Y., N.Y., 1980 (ISBN 0-8247-6918-X).

Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and

programmed release.

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Verma *et al*, Pharmaceutical Technology On-line, 25(2), 5 1-14 (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

PARENTERAL ADMINISTRATION

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, 10 intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from about 3 to about 9), but, for some 15 applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilization, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

20 The solubility of compounds of formula (I) used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and 25 programmed release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and PGLA microspheres.

TOPICAL ADMINISTRATION

30 The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibers, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene 35 glycol. Penetration enhancers may be incorporated - see, for example, *J Pharm Sci*, 88 (10), 955-958 by Finnin and Morgan (October 1999).

Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (e.g. Powderject™, Bioject™, etc.) injection.

40 Formulations for topical administration may be formulated to be immediate and/or modified

release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

INHALED/INTRANASAL ADMINISTRATION

5 The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurized container, pump, spray, atomizer (preferably an atomizer using electrohydrodynamics to produce a fine mist), or nebulizer, with or without the use of a
10 suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurized container, pump, spray, atomizer, or nebulizer contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilizing, or extending release of the active, a propellant(s) as
15 solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronized to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenization, or spray drying.

20 Capsules (made, for example, from gelatin or HPMC), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as *L*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and
25 trehalose.

A suitable solution formulation for use in an atomizer using electrohydrodynamics to produce a fine mist may contain from about 1 μ g to about 20mg of the compound of the invention per actuation and the actuation volume may vary from about 1 μ l to about 100 μ l. A typical formulation may comprise a compound of formula (I), propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents
30 which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavors, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration. Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, poly(DL-lactic-coglycolic acid (PGLA). Modified release
35 formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing from about 1 to about 100 μ g of the compound of formula (I). The overall daily dose will typically be in the range about 50 μ g to about 20 mg which may be
40 administered in a single dose or, more usually, as divided doses throughout the day.

RECTAL/INTRAVAGINAL ADMINISTRATION

The compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various
5 alternatives may be used as appropriate.

Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

10

OCULAR/AURAL ADMINISTRATION

The compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronized suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (e.g.
15 absorbable gel sponges, collagen) and non-biodegradable (e.g. silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as
20 benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

Formulations for ocular/aural administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted, or programmed release.

25 OTHER TECHNOLOGIES

The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

30 Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, i.e. as a carrier, diluent, or solubilizer. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in. WO 91/11172, WO 94/02518 and WO
35 98/55148.

KIT-OF-PARTS

Inasmuch as it may be desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention
40 that two or more pharmaceutical compositions, at least one of which contains a compound in accordance

with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions.

Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of formula (I) in accordance with the invention, and means for 5 separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically 10 comprises directions for administration and may be provided with a so-called memory aid.

DOSAGE

For administration to human patients, the total daily dose of the compounds of the invention is typically in the range of about 0.05 mg to about 100 mg depending, of course, on the mode of administration, preferred in the range of about 0.1 mg to about 50 mg and more preferred in the range of 15 about 0.5 mg to about 20 mg. For example, oral administration may require a total daily dose of from about 1 mg to about 20 mg, while an intravenous dose may only require from about 0.5 mg to about 10 mg. The total daily dose may be administered in single or divided doses.

These dosages are based on an average human subject having a weight of about 65kg to about 70kg. The physician will readily be able to determine doses for subjects whose weight falls outside this 20 range, such as infants and the elderly.

As discussed above, a compound of the invention exhibits CB2 agonist activity. A CB2 agonist of the present invention may be usefully combined with another pharmacologically active compound, or with two or more other pharmacologically active compounds, particularly in the treatment of the cancer, inflammatory diseases, immunomodulatory diseases and gastrointestinal disorder. For example, a CB2 25 agonist, particularly a compound of the formula (I), or a pharmaceutically acceptable salt thereof, as defined above, may be administered simultaneously, sequentially or separately in combination with one or more agents selected from:

- (i) 5-HT₃ antagonists, e.g. dolasetron, palonosetron, alosetron, azasetron and ramosetron, mitrazapine, granisetron, tropisetron, E-3620, ondansetron and indisetron;
- 30 (ii) 5-HT₄ agonists, e.g. tegaserod, mosapride, cinitapride and oxatriptane;
- (iii) opioid analgesics, e.g. morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, naloxefene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine Modulon[®](trimebutine malate), Imodium[®] (loperamide) and pentazocine;
- 35 (iv) tricyclic antidepressants, e.g. imipramine, amitriptyline, clomipramine, amoxapine and lofepramine;
- (v) somatostatin analogues, e.g. octreotide, AN-238 and PTR-3173;
- (vi) anticholinergics, e.g. dicyclomine and hyoscyamine, ipratropium bromide, ipratropium, tiotropium bromide;
- 40 (vii) laxatives, e.g. Trifyba[®], Fybogel[®], Konsyl[®], IsoGel[®], Regulan[®], Celevac[®] and Normacol[®];

- (viii) fiber products, e.g. Metamucil®;
- (ix) antispasmodics, e.g.: mebeverine;
- (x) dopamine antagonists, e.g. metoclopramide, domperidone and levosulpiride;
- (xi) cholinergics, e.g. neostigmine, pilocarpine, carbachol
- 5 (xii) calcium channel blockers, e.g. aranidipine, lacidipine, falodipine, azelnidipine, clinidipine, lomerizine, diltiazem, gallopamil, efondipine, nisoldipine, amlodipine, lercanidipine, bevantolol, nicardipine, isradipine, benidipine, verapamil, nitrendipine, barnidipine, propafenone, manidipine, bepridil, nifedipine, nilvadipine, nimodipine and fasudil;
- (xiii) Cl Channel activator: e.g. lubiprostone;
- 10 (xiv) selective serotonin reuptake inhibitors, e.g. sertraline, escitalopram, fluoxetine, nefazodone, fluvoxamine, citalopram, milnacipran, paroxetine, venlafaxine, tramadol, sibutramine, duloxetine, desvenlafaxine and depoxetine;
- (xv) GABA agonists, e.g. gabapentin, topiramate, cinolazepam, clonazepam, progabide, brotizolam, zopiclone, pregabalin and eszopiclone;
- 15 (xvi) tachykinin (NK) antagonists, particularly NK-3, NK-2 and NK-1 antagonists, e.g.: nepadutant, saredutant, talnetant, (α R,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7]naphthridine-6-13-dione (TAK-637), 5-[[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (MK-869), lanepitant, dapitant and 3-[[2-methoxy-5-(trifluoromethoxy)phenyl]methylamino]-2-phenyl-piperidine (2S,3S).
- 20 (xvii) α 2 agonists, e.g. clonidine, medetomidine, lofexidine, moxonidine, tizanidine, guanfacine, guanabenz, talipexole and dexmedetomidine;
- (xviii) benzodiazepine agonists, e.g. diazepam, zaleplon, zolpidem, haloxazolam, clonazepam, prazepam, quazepam, flutazolam, triazolam, lormetazepam, midazolam, tofisopam, clobazam, flunitrazepam and flutoprazepam;
- 25 (xix) prostaglandin analogues, e.g. Prostaglandin, misoprostol, treprostinil, esoprostenol, latanoprost, iloprost, beraprost, enprostil, ibudilast and ozagrel;
- (xx) histamine H₃ agonists, e.g. R-alpha-methylhistamine and BP-294;
- 30 (xxi) anti-gastric agents, e.g. Anti-gastrin vaccine, itriglumide and Z-360;
- (xxii) disease modifying anti-rheumatic drugs (DMARDs), e.g. methotrexate, leflunomide, penicillamine aurothiopropanol sulfonate, sulfasalazine, mesalamine, olsalazine, balsalazide, Hylan G-F 20, glucosamine, chondroitin sulfate, hydroxychloroquine and diacerein.
- 35 (xxiii) Tumor Necrosis Factor-Alpha(TNF- α) modulators, e.g. etanercept, infliximab, adalimumab, CDP-870, pegsunercept, ISIS-104838, RDP-58 and thalidomide;
- (xxiv) interleukin-based therapies, e.g. anakinra, atlizumab, RGN-303, denileukin diftitox, ilodecakin, oprelvekin and mepolizumab;
- 40 (xxv) nonsteroidal antiinflammatory drugs (NSAIDs), e.g. piroxicam, naproxen, indomethacin, ibuprofen, diclofenac, ketorolac, flurbiprofen, aspirin, diflusinal, etodolac, fenbufen, fenoprofen, flufenisal, ketoprofen, meclofenamic acid, mefenamic acid, nabumetone, oxaprozin, phenylbutazone, sulindac,

- tolmetin and zomepirac;
- (xxvi) selective COX-2 Inhibitors, e.g. celecoxib, rofecoxib, valdecoxib, etoricoxib, lumiracoxib and LAS-34475;
- (xxvii) Centrally Acting Analgesics, e.g. tramadol and oxymorphone ER;
- 5 (xxviii) immunosuppressives, e.g. cyclosporine, tacrolimus, rapamycin, azathioprine and mycophenolate mofetil;
- (xxix) Multiple Sclerosis(MS) treatments, e.g. interferon β -1b, interferon β -1a, glatiramer acetate, mitoxantrone, cyclophosphamide, MBP-8298, AG-284, tiplimotide, BX-471, E-2007, recombinant glial growth factor-2 and natalizumab;
- 10 (xxx) Monoclonal Antibodies, e.g. natalizumab, daclizumab, alemtuzumab, omalizumab, TNX-100 and SGN-40;
- (xxxi) insulin secretagogues, e.g. glyburide, glipizide, repaglinide and glimiperide;
- (xxxii) biguanides, e.g. metformin;
- (xxxiii) alpha-glucosidase inhibitors, e.g. acarbose, voglibose and miglitol;
- 15 (xxxiv) PPAR γ agonists, e.g. pioglitazone and rosiglitazone;
- (xxxv) antibiotics, e.g. sulfacetamide, erythromycin, gentamicin, tobramycin, ciprofloxacin and ofloxacin
- (xxxvi) cell adhesion molecule inhibitors , e.g. alicaforsen, MLN-02, alefacept, efalizumab, R-411 and IVL-745;
- (xxxvii) anti-allergy drugs, e.g. levocabastine, olopatadine, cromolyn, Iodoxamide , pheniramine,
- 20 ketotifen, mizolastine and epinastine;
- (xxxviii) ophthalmologic anti-virals, e.g. adenine arabinoside and idoxuridine;
- (xxxix) glaucoma treatments, e.g. timolol, metipranolol, carteolol, betaxolol, levobunolol, brimonidine, iopidine, dorzolamide, epinephrine and dipivefrin;
- (xl) alkylating anti-tumor agents, e.g. busulfan, carboplatin, chlorambucil, cisplatin, cyclophosphamide,
- 25 dacarbazine, ifosfamide, mechlorethamine , melphalan, procarbazine, thiotepa, and uracil mustard;
- (xli) nitrosoureas, e.g. carmustine, lomustine and streptozocin;
- (xlii) antimetabolites, e.g. 5-fluorouracil, 6-mercaptopurine, capecitabine, cytosine arabinoside, flouxuridine, fludarabine, gemcitabine, methotrexate, thioguanine and azathioprine;
- (xliii) antitumor biotics, e.g. dactinomycin, daunorubicin, doxorubicin, idarubicin, mitomycin-C, and
- 30 mitoxantrone;
- (xliv) anti-microtubule agents, e.g. vinblastine, vincristine, vindesine, vinorelbine, paclitaxel and docetaxel;
- (xlv) vitamine derivatives, e.g. calcipotriol and tacalcitol;
- (xlvi) leukotriene antagonists, e.g. montelukast, zafirlukast and pranlukast;
- 35 (xlvii) β 2 Agonists, e.g. albuterol, levalbuterol, salmeterol, formoterol and arformoterol;
- (xlviii) corticosteroids, e.g. prednisone, ciclesonide, budesonide, fluticasone , methylprednisolone, hydrocortisone and BP-1011;
- (xlix) methylxanthines, e.g. theophylline, aminophylline and doxophylline;
- (l) asthma and/or COPD treatments, e.g. roflumilast, tiotropium, israpafant, N-acetylcysteine and
- 40 α 1-antitrypsin;

- (ii) a vanilloid receptor agonist (e.g. resiniferatoxin) or antagonist (e.g. capsazepine);
- (iii) an alpha-2-delta ligand such as gabapentin, pregabalin, 3-methylgabapentin, (1 α ,3 α ,5 α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-octanoic acid, (2S,4S)-4-(3-chlorophenoxy)proline, (2S,4S)-4-(3-fluorobenzyl)-proline, [(1R,5R,6S)-6-(aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1-(1H-tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid, (3S,5R)-3-amino-5-methyl-octanoic acid, (3R,4R,5R)-3-amino-4,5-dimethyl-heptanoic acid and (3R,4R,5R)-3-amino-4,5-dimethyl-octanoic acid; and
- (liii) a prostaglandin E₂ subtype 4 (EP4) antagonist such as N-[(2-[4-(2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl)amino]-carbonyl]-4-methylbenzenesulfonamide or 4-[(1S)-1-((5-chloro-2-(3-fluorophenoxy)pyridin-3-yl)carbonyl)amino]ethyl]benzoic acid.

Method for assessing biological activities:

The CB2 receptor binding affinity and other biological activities of the compounds of this invention are determined by the following procedures.

20

Rat CB2 binding

Rat spleen cells were placed in tissue preparation buffer [5 mM Tris-HCl (pH7.4 at 25°C) and 2 mM EDTA] and homogenized using a hand held Polytron PT1200CL disruptor set at 25,000 rpm for 30 seconds on ice, then kept on ice for 15 min. The homogenates were centrifuged at 1,000 x g at 4°C for 10 min. The supernatant was recovered and centrifuged at 40,000 x g at 4°C for 10 min. The pellets were then resuspended in 50 mM Tris-HCl (pH7.4 at 25°C). This suspension was centrifuged once more in the same manner. The final pellet was resuspended in TME buffer (25 mM Tris-HCl (pH7.4), 5 mM MgCl₂, 1 mM EDTA, 0.5% BSA), aliquoted and stored at -80°C until assayed. An aliquot was used for the determination of protein concentration using BCA™ protein assay kit (PIERCE) and the measurement was made on Wallac 1420 ARVOsx multilabel counter with BSA as a standard.

For the binding experiments, 20 μ L of test compounds were incubated with 20 μ L of [³H]CP55,940 (Perkin Elmer, final 1 nM) and 160 μ L of membrane homogenate (1 μ g protein/ tube) for 60 minutes at 37°C. Nonspecific binding was determined by 1 μ M CP55,940 (TOCRIS Cookson Inc) at the final concentration. All incubations were harvested by vacuum filtration through GF/B fiber filters pre-soaked in 5% BSA in TME buffer using Uni-Filter cell harvester (Packard). Filters were rinsed with wash buffer (25 mM Tris-HCl (pH7.4), 5 mM MgCl₂, 1 mM EDTA) and then dried up at 50°C for 30 min. The radioactivity was measured by scintillation counting using Top-Count Microplate Scintillation Counter (Packard). Rat CB1 binding affinities were also determined by a method similar to the above by using rat whole brains.

40

All compounds of Examples showed selective CB2 receptor affinity.

Human CB2 binding

Human CB2 transfected Chinese hamster ovary K1 (CHO-K1) cells were established and grown to 60-80 % confluence. The collected cell pastes were washed with cold PBS, suspended in 50 mM Tris-HCl (pH7.4 at 25°C) containing protease inhibitor cocktail and homogenized using a hand held

- 5 Polytron PT 1200 disruptor set at 25,000 rpm for 30 seconds on ice. The homogenates were centrifuged at 1,000 x g at 4°C for 10 min. The supernatant was recovered and centrifuged at 40,000 x g at 4°C for 10 min. The pellets were then resuspended in 50 mM Tris-HCl (pH7.4 at 25°C). This suspension was centrifuged once more in the same manner. The final pellet was resuspended in TME buffer (25 mM Tris-HCl (pH7.4), 5 mM MgCl₂, 1 mM EDTA, 0.5% BSA), aliquoted and stored at -80°C until assayed. An
10 10 aliquot was used for the determination of protein concentration using BCA™ protein assay kit (PIERCE) and the measurement was made on Wallac 1420 ARVOsx multilabel counter with BSA as a standard.

For the binding experiments, 20 µL of test compounds were incubated with 20 µL of [³H] CP55,940 (Perkin Elmer, final 1 nM) and 160 µL of membrane homogenate (1 µg protein/ tube) for 60 minutes at 37°C. Nonspecific binding was determined by 1 µM CP55,940 (TOCRIS Cookson Inc) at the
15 final concentration.

All incubations were harvested by vacuum filtration through GF/B fiber filters pre-soaked in 5% BSA in TME buffer using Uni-Filter cell harvester (Packard). Filters were rinsed with wash buffer (25 mM Tris-HCl (pH7.4), 5 mM MgCl₂, 1 mM EDTA) and then dried up at 50°C for 30 min. The radioactivity was measured by scintillation counting using Top-Count Microplate Scintillation Counter (Packard). Human
20 CB1 binding affinities were also determined by a method similar to the above by using Human CB1 transfected Chinese hamster ovary-K1(CHO-K1) cells, [³H]SR141716A(Amersham Bioscience) and AM251(TOCRIS Cookson Inc).

All compounds of Examples showed selective CB2 receptor affinity.

25 **Agonist-induced cAMP change in human CB2 transfected CHO-K1 cells**

Human CB2 transfected Chinese hamster ovary-K1 (CHO-K1) cells were established and grown to 60-80 % confluence. The medium was changed to F-12 medium containing 10 % dialysed FBS, and the cells were incubated overnight. On the day of the assay, the cells were harvested with PBS/1mM EDTA, centrifuged and washed with PBS. Cell pellets were resuspended in the incubation buffer (F-12
30 medium, 20 mM HEPES, 1 mM IBMX, 0.1 mM Ro-20-1724) at the concentration of 1x 10⁵ cells/ml and pre-incubated for 15 min at room temperature. The agonist samples were diluted from 10 mM stock solution in DMSO and dispensed into 96-well half-area plates (12.5 µL/well) with assay buffer (F-12, 20 mM HEPES). The reaction was initiated by adding the cells (25 µL/well) into the well containing forskolin (12.5 µL/well, final 5 µM) and diluted compounds. After incubation for 30 minutes at 37°C, cAMP-XL665
35 conjugated, and then the anti-cAMP-cryptase conjugate was added to the lysate (25 µL/well each). After further incubation for 60 minutes at room temperature, measurements were made on the Wallac 1420 ARVOsx multilabel counter (Excitation 320 nm, Emission 665 nm/620 nm, delay time 50 µs, window time 400 µs). Data analysis was made based on the ratio of fluorescence intensity of each well at 620 nm and 665 nm. The equation "sigmoidal dose-response" was used for the determination of EC₅₀ and Emax
40 values.

All compounds of Examples showed CB2 receptor agonistic activity.

Human dofetilide binding

Human HERG transfected HEK293S cells were prepared and grown in-house. The collected cells

5 were suspended in 50 mM Tris-HCl (pH 7.4 at 4°C) and homogenized using a hand held Polytron PT 1200 disruptor set at full power for 20 sec on ice. The homogenates were centrifuged at 48,000 x g at 4 °C for 20 min. The pellets were then resuspended, homogenized, and centrifuged once more in the same manner. The final pellets were resuspended in an appropriate volume of 50 mM Tris-HCl, 10 mM KCl, 1 mM MgCl₂ (pH 7.4 at 4°C), homogenized, aliquoted and stored at -80°C until use. An aliquot of
10 membrane fractions was used for protein concentration determination using BCA protein assay kit (PIERCE) and ARVOsx plate reader (Wallac).

Binding assays were conducted in a total volume of 200 µL in 96-well plates. Twenty µL of test compounds were incubated with 20 µL of [³H]-dofetilide (Amersham, final 5 nM) and 160 µL of membrane homogenate (25 µg protein) for 60 minutes at room temperature. Nonspecific binding was determined by
15 10 µM dofetilide at the final concentration. Incubation was terminated by rapid vacuum filtration over 0.5% presoaked GF/B Betaplate filter using Skatron cell harvester with 50 mM Tris-HCl, 10 mM KCl, 1 mM MgCl₂, pH 7.4 at 4°C. The filters were dried, put into sample bags and filled with Betaplate Scint. Radioactivity bound to filter was counted with Wallac Betaplate counter.

20 **Caco-2 permeability**

Caco-2 permeability was measured according to the method described in Shiycin Yee, *Pharmaceutical Research*, 763 (1997).

Caco-2 cells were grown on filter supports (Falcon HTS multiwell insert system) for 14 days. Culture medium was removed from both the apical and basolateral compartments and the monolayers
25 were preincubated with pre-warmed 0.3 ml apical buffer and 1.0 ml basolateral buffer for 0.5 hour at 37°C in a shaker water bath at 50 cycles/min. The apical buffer consisted of Hanks Balanced Salt Solution, 25 mM D-glucose monohydrate, 20 mM MES Biological Buffer, 1.25 mM CaCl₂ and 0.5 mM MgCl₂ (pH 6.5). The basolateral buffer consisted of Hanks Balanced Salt Solution, 25 mM D-glucose monohydrate, 20 mM HEPES Biological Buffer, 1.25 mM CaCl₂ and 0.5 mM MgCl₂ (pH 7.4). At the end of the
30 preincubation, the media was removed and test compound solution (10µM) in buffer was added to the apical compartment. The inserts were moved to wells containing fresh basolateral buffer at 1 hr. Drug concentration in the buffer was measured by LC/MS analysis.

Flux rate (F, mass/time) was calculated from the slope of cumulative appearance of substrate on the receiver side and apparent permeability coefficient (P_{app}) was calculated from the following equation.

35
$$P_{app} \text{ (cm/sec)} = (F * VD) / (SA * MD)$$

where SA is surface area for transport (0.3 cm²), VD is the donor volume (0.3ml), MD is the total amount of drug on the donor side at t = 0. All data represent the mean of 2 inserts. Monolayer integrity was determined by Lucifer Yellow transport.

40 **Half-life in human liver microsomes (HLM)**

Test compounds (1 µM) were incubated with 3.3 mM MgCl₂ and 0.78 mg/mL HLM (HL101) in

100 mM potassium phosphate buffer (pH 7.4) at 37°C on the 96-deep well plate. The reaction mixture was split into two groups, a non-P450 and a P450 group. NADPH was only added to the reaction mixture of the P450 group. An aliquot of samples of P450 group was collected at 0, 10, 30, and 60 min time point, where 0 min time point indicated the time when NADPH was added into the reaction mixture of 5 P450 group. An aliquot of samples of non-P450 group was collected at -10 and 65 min time point. Collected aliquots were extracted with acetonitrile solution containing an internal standard. The precipitated protein was spun down in centrifuge (2000 rpm, 15 min). The compound concentration in supernatant was measured by LC/MS/MS system.

The half-life value was obtained by plotting the natural logarithm of the peak area ratio of 10 compounds/ internal standard versus time. The slope of the line of best fit through the points yields the rate of metabolism (k). This was converted to a half-life value using following equations:

$$\text{Half-life} = \ln 2 / k$$

TNBS-induced chronic colonic allodynia in the rat

15 Male IGS (Sprague-Dawley) rats, 240-270 g (7 weeks, Charles River Japan) are used. Environment conditions are controlled at a 12-h light/dark cycle with lights on at 07:00 and an ambient temperature of 23+/-2°C. Rats are housed under this condition for 4 days before the surgery. Each group is used a group of 6-8 rats. Rats are fasted for 24 hours before use. After weighing and administration of 20 the anesthetic (Ketamine/Xylazine), the animal is placed in the dorsal decubitus position. The abdomen is shaved and disinfected with 10 % povidoneiodine solution (isodine). A 2-cm long median laparotomy is conducted by making the incision 3 cm from the sternum. The cecum is then found, grasped with the fingers, removed from the abdominal cavity and placed on a compress that has been previously moistened with isotonic saline. TNBS (Fluka; 50 mg/kg; 1.5 ml/kg in 30 % EtOH) is injected into the proximal colon (1 cm from the cecum). Sham group's animal undergoes the same surgery but TNBS is 25 not injected. After injection, the intestines are put back into the abdominal cavity. The muscle wall is then sutured with silk, using two cross-stitches. The skin is also sutured. After 7 days from the surgery, the balloon (5 cm in length) is inserted through the anus and kept in position (tip of balloon is 5 cm from the anus) by taping the catheter to the base of the tail. The animals are individually placed without restraint in cages for distention session. The balloon is progressively inflated by step of 5 mm Hg, from 0 to 70 mm 30 Hg, each step of inflation lasting 30s. Each cycle of colonic distention is controlled by a standard barostat (G&J Electronic Inc. CANADA). The pain threshold corresponds to the pressure that produced the first abdominal contraction. The abdominal contraction corresponds to waves of contraction of oblique musculature with inward turning of the hindlimb, or to humpbacked position, or to squashing of the lower abdomen against the floor (Wesselmann U et al., (1998) Neurosci Lett 246: 73-76). To determine the 35 basal colonic threshold, two cycles of distention are performed on the same animal with an interval of >10 min before compound administration. The 1st distention is conducted to acclimate the rat to the colonic distention. The baseline is determined by the second distention. The effect of a test compound on the colonic threshold is investigated at X min post dosing. If necessary, the time course of effect of a test compound may be studied at different times.

40 Distribution of the treatment groups is as follows:

| | Injection of TNBS | Treatment |
|--------------------|-------------------|---------------|
| Sham control group | No | Vehicle |
| TNBS control group | Yes | Vehicle |
| Treated group | Yes | Test compound |

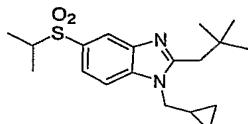
The data are expressed as median threshold (mmHg) required to induce abdominal contractions in each group (vertical bars represent 1st and 3rd quartiles). Data are analyzed using Kruskal-Wallis test followed by Mann-Whitney U-test.

5 Examples

The invention is illustrated in the following non-limiting examples in which, unless stated otherwise: all reagents are commercially available, all operations were carried out at room or ambient temperature, that is, in the range of about 18-25 °C; evaporation of solvent was carried out using a rotary evaporator under reduced pressure with a bath temperature of up to about 60 °C; reactions were monitored by thin layer chromatography (tlc) and reaction times are given for illustration only; melting points (m.p.) given are uncorrected (polymorphism may result in different melting points); the structure and purity of all isolated compounds were assured by at least one of the following techniques: tlc (Merck silica gel 60 F₂₅₄ precoated TLC plates or Merck NH₂ F_{254s} precoated HPTLC plates), mass spectrometry, nuclear magnetic resonance (NMR), infrared red absorption spectra (IR) or microanalysis. Yields are given for illustrative purposes only. Flash column chromatography was carried out using Merck silica gel 60 (230-400 mesh ASTM) or Fuji Silysia Chromatorex® DU3050 (Amino Type, 30~50 µm). Low-resolution mass spectral data (EI) were obtained on a Integrity (Waters) mass spectrometer or a Automass 120 (JEOL) mass spectrometer. Low-resolution mass spectral data (ESI) were obtained on a ZMD2 (Waters) mass spectrometer or a Quattro II (Micromass) mass spectrometer. NMR data was determined at 270 MHz (JEOL JNM-LA 270 spectrometer) or 300 MHz (JEOL JNM-LA300) using deuterated chloroform (99.8% D) or dimethylsulfoxide (99.9% D) as solvent unless indicated otherwise, relative to tetramethylsilane (TMS) as internal standard in parts per million (ppm); conventional abbreviations used are: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, etc. IR spectra were measured by a Shimazu infrared spectrometer (IR-470). Optical rotations were measured using a JASCO DIP-370 Digital Polarimeter (Japan Spectroscopic Co., Ltd.). Chemical symbols have their usual meanings; b.p. (boiling point), m.p. (melting point), L(liter(s)), mL (milliliter(s)), g (gram(s)), mg(milligram(s)), mol (moles), mmol (millimoles), eq. (equivalent(s)).

Example 1

30 1-(Cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-(isopropylsulfonyl)-1*H*-benzimidazole



Step A. 1-Chloro-4-(isopropylthio)benzene

To a solution of 4,4'-dichlorodiphenyl disulfide (Tokyo Kasei Kogyo Co., Ltd., 1 g, 3.5 mmol) in ethanol (10 mL) and tetrahydrofuran (10 mL) was added sodium borohydride (473 mg, 12.5 mmol) at 0 °C.

After stirring at 0 °C for 30 min, 2-iodopropane (833 µL, 8.4 mmol) was added and the mixture was stirred at 0 °C for 30 min and at room temperature for 3 h. Water (30 mL) was added and the mixture was extracted with hexane (30 mL x 3). The organic extracts were dried over sodium sulfate and concentrated to afford the title compound (1.3 g, 100%) as colorless oil.

5 $^1\text{H-NMR}$ (CDCl_3) δ:7.35-7.25 (m, 4H), 3.41-3.26 (m, 1H), 1.28 (d, $J= 6.6$ Hz, 6H).

Step B. 1-Chloro-4-(isopropylsulfonyl)benzene

To a solution of 1-chloro-4-(isopropylthio)benzene (Step A, 0.6 g, 3.2 mmol) in dichloromethane (25 mL) was added m-chloroperbenzoic acid (1.6g, 6.4 mmol) portionwise at 0 °C. The mixture was stirred at 0 °C for 1 h. Aqueous sodium sulfide (15 mL) and aqueous ammonia (15 mL) were added.

10 The mixture was extracted with dichloromethane (15 mL x 2) and washed with aqueous ammonia (15 mL) and water (15 mL). The organic extracts were dried over sodium sulfate and concentrated to afford the title compound (679 mg, 97%) as a white solid.

$^1\text{H-NMR}$ (CDCl_3) δ:7.85-7.80 (m, 2H), 7.57-7.53 (m, 2H), 3.24-3.14 (m, 1H), 1.30 (d, $J= 6.9$ Hz, 6H).

Step C. 1-Chloro-4-(isopropylsulfonyl)-2-nitrobenzene

15 To a solution of 1-chloro-4-(isopropylsulfonyl)benzene (Step B, 679 mg, 3.1 mmol) in sulfuric acid (3 mL) was added potassium nitrate (555 mg, 5.5 mmol) at 80 °C. The mixture was stirred at 90 °C for 2 h. Ice water (5 mL) was added, and the mixture was extracted with ethyl acetate (25 mL) and washed with water (10 mL x 2) and brine (10 mL). The organic extracts were dried over sodium sulfate and concentrated to afford the title compound (849 mg, containing ethyl acetate) as a white solid.

20 $^1\text{H-NMR}$ (CDCl_3) δ:8.37 (d, $J= 2.0$ Hz, 1H), 8.02 (dd, $J= 8.3, 2.0$ Hz, 1H), 7.80 (d, $J= 8.3$ Hz, 1H), 3.33-3.20 (m, 1H), 1.35 (d, $J= 7.0$ Hz, 6H).

Step D. N-(Cyclopropylmethyl)-4-(isopropylsulfonyl)-2-nitroaniline

A mixture of 1-chloro-4-(isopropylsulfonyl)-2-nitrobenzene (Step C, 849 mg, 3.2 mmol), and cyclopropylmethylamine (333 µL, 3.8 mmol) in ethanol (15 mL) was stirred under reflux for 16 h. After 25 removal of solvent, the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 3/1 as eluent) to afford the title compound (521 mg, 55%) as a yellow solid.

$^1\text{H-NMR}$ (CDCl_3) δ:8.70 (d, $J= 2.2$ Hz, 1H), 8.50 (br s, 1H), 7.82 (dd $J= 9.1, 2.2$ Hz, 1H), 6.93 (d, $J= 9.1$ Hz, 1H), 3.25-3.13 (m, 3H), 1.31 (d, $J= 6.8$ Hz, 6H), 1.27-1.16 (m, 1H), 0.74-0.67 (m, 2H), 0.39-0.34 (m, 2H).

30 MS (ESI) 299 ($M + H$)⁺.

Step E. 2-Amino-1-(N-cyclopropylmethylamino)- 4-(isopropylsulfonyl)benzene

A mixture of *N*-(cyclopropylmethyl)-4-(isopropylsulfonyl)-2-nitroaniline (Step D, 521 mg, 1.8 mmol) and 10% palladium carbon (52 mg) in methanol (10 mL) and ethyl acetate (10 mL) was stirred at room temperature for 2 h under hydrogen. The mixture was filtered through a pad of celite and the 35 filtrate was concentrated to afford the title compound (462 mg, 98%) as red brown amorphous.

$^1\text{H-NMR}$ (CDCl_3) δ:7.33 (dd, $J= 8.4, 2.0$ Hz, 1H), 7.17 (d, $J= 2.0$ Hz, 1H), 6.62 (d, $J= 8.4$ Hz, 1H), 4.10 (br, 1H), 3.40 (br s, 2H), 3.20-3.05 (m, 1H), 3.02 (dd, $J= 6.9, 5.3$ Hz, 2H), 1.27 (d, $J= 6.9$ Hz, 6H), 1.21-1.08 (m, 1H), 0.65-0.58 (m, 2H), 0.32-0.26 (m, 2H) .

MS (ESI) 269($M + H$)⁺, 267 ($M - H$)⁻.

40 Step F. 1-(Cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-(isopropylsulfonyl)-1*H*- benzimidazole

To a solution of 2-amino-1-(*N*-cyclopropylmethylamino)-4- (isopropylsulfonyl)benzene (Step E, 113 mg, 0.38 mmol) in ethyl acetate (3 mL) was added *tert*-butylacetyl chloride (58 μ L, 0.42 mmol) at room temperature. After stirring for 1 h, *p*-toluenesulfonic acid monohydrate (72 mg, 0.38 mmol) was added and the mixture was stirred under reflux for 3 h. Water (5 mL) and aqueous ammonia (0.5 mL) were added and the mixture was extracted with ethyl acetate (15 mL x 3) and washed with brine (5 mL). The organic extracts were dried over sodium sulfate and concentrated. The residue was purified by pTLC (hexane : ethyl acetate = 1 : 1 then dichloromethane : methanol = 10 : 1 as eluent) to give colorless oil (74 mg), which was recrystallized from ethyl acetate and hexane to afford the title compound (28 mg, 21%) as a white solid.

10 $^1\text{H-NMR}$ (CDCl_3) δ : 8.28 (d, J = 1.7 Hz, 1H), 7.76 (dd, J = 8.5, 1.7 Hz, 1H), 7.48 (d, J = 8.5 Hz, 1H), 4.12 (d, J = 6.6 Hz, 2H), 3.29-3.19 (m, 1H), 2.85 (s, 2H), 1.31 (d, J = 7.0 Hz, 6H), 1.25-1.16 (m, 1H), 1.11 (s, 9H), 0.67-0.61 (m, 2H), 0.42-0.37 (m, 2H).

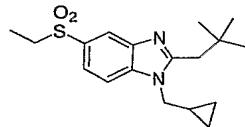
MS (ESI) 349 ($M + H$) $^+$.

m.p. 139 °C

15

Example 2

1-(Cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-(ethylsulfonyl)-1*H*-benzimidazole and its hydrochloride salt



20 Step A. 1-Chloro-4-(ethylthio)benzene

The title compound was prepared according to the procedure described in Step A of Example 1 from 4,4'-dichlorodiphenyl disulfide and ethyl iodide.

$^1\text{H-NMR}$ (CDCl_3) δ : 7.25 (s, 4H), 2.92 (q, J = 7.3 Hz, 2H), 1.30 (t, J = 7.3 Hz, 3H).

Step B. 1-Chloro-4-(ethylsulfonyl)benzene

25 The title compound was prepared according to the procedure described in Step B of Example 1 using 1-chloro-4-(ethylthio)benzene (Step A) instead of 1-chloro-4-(isopropylthio)benzene.

$^1\text{H-NMR}$ (CDCl_3) δ : 7.85 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.5 Hz, 2H), 3.12 (q, J = 7.4 Hz, 2H), 1.29 (t, J = 7.4 Hz, 3H).

Step C. 1-Chloro-4-(ethylsulfonyl)-2-nitrobenzene

30 The title compound was prepared according to the procedure described in Step C of Example 1 using 1-chloro-4-(ethylsulfonyl)benzene (Step B) instead of 1-chloro-4-(isopropylsulfonyl)benzene.

$^1\text{H-NMR}$ (CDCl_3) δ : 8.40 (d, J = 2.2 Hz, 1H), 8.07-8.03 (m, 1H), 7.80 (d, J = 8.2 Hz, 1H), 3.19 (q, J = 7.4 Hz, 2H), 1.34 (t, J = 7.4 Hz, 3H).

Step D. N-(Cyclopropylmethyl)-4-(ethylsulfonyl)-2-nitroaniline

35 The title compound was prepared according to the procedure described in Step D of Example 1 using 1-chloro-4-(ethylsulfonyl)-2-nitrobenzene (Step C) instead of 1-chloro-4-(isopropylsulfonyl)-2-nitrobenzene.

¹H-NMR (CDCl₃) δ:8.73 (d, J= 2.2 Hz, 1H), 8.51 (br s, 1H), 7.85 (dd J= 9.1, 2.2 Hz, 1H), 6.94 (d, J= 9.1 Hz, 1H), 3.23 (dd, J= 7.1, 4.9 Hz, 2H), 3.11 (q, J= 7.4 Hz, 2H), 1.30 (t, J= 7.4 Hz, 3H), 1.26-1.17 (m, 1H), 0.74-0.68 (m, 2H), 0.39-0.34 (m, 2H) .

MS (ESI) 285 (M + H)⁺, 283 (M - H)⁻.

5 Step E. 2-Amino-1-(N-cyclopropylmethylamino)-4-(ethylsulfonyl)benzene

The title compound was prepared according to the procedure described in Step E of Example 1 using N-(cyclopropylmethyl)-4-(ethylsulfonyl)-2-nitroaniline (Step D) instead of N-(cyclopropylmethyl)-4-(isopropylsulfonyl)-2-nitroaniline.

10 ¹H-NMR (CDCl₃) δ:7.36 (dd, J= 8.4, 2.1 Hz, 1H), 7.19 (d, J= 2.1 Hz, 1H), 6.62 (d, J= 8.4 Hz, 1H), 3.09-3.01 (m, 4H), 1.24 (t, J= 7.3 Hz, 3H), 1.20-1.09 (m, 1H), 0.64-0.58 (m, 2H), 0.31-0.26 (m, 2H), peaks of NH and NH₂ were not observed.

MS (ESI) 255 (M + H)⁺, 253 (M - H)⁻.

Step F. 1-(Cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-(ethylsulfonyl)-1*H*-benzimidazole hydrochloride

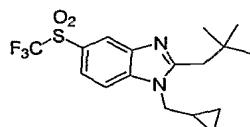
The title compound was prepared according to the procedure described in Step F of Example 1 using 2-amino-1-(N-cyclopropylmethylamino)-4-(ethylsulfonyl)benzene (Step E) instead of 2-amino-1-(N-cyclopropylmethylamino)-4-(isopropylsulfonyl)benzene. Obtained 1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-(ethylsulfonyl)-1*H*-benzimidazole was dissolved in ethyl acetate and to the solution was added 4 N hydrogen chloride in ethyl acetate. The precipitate was collected by filtration to afford the title compound as a white solid.

20 ¹H-NMR (CDCl₃) δ:8.65 (br s, 1H), 8.05-8.02 (m, 1H), 7.80-7.77 (m, 1H), 4.32-4.29 (m, 2H), 3.27 (s, 2H), 3.23-3.17 (m, 2H), 1.32-1.23 (m, 4H), 1.20 (s, 9H), 0.82-0.76 (m, 2H), 0.53-0.47 (m, 2H) .
MS (ESI) 335 (M + H)⁺.

m.p. 191 °C

25 **Example 3**

1-(Cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-[(trifluoromethyl)sulfonyl]-1*H*-benzimidazole



Step A. N-(Cyclopropylmethyl)-2-nitro-4-[(trifluoromethyl)sulfonyl]aniline

The title compound was prepared according to the procedure described in Step D of Example 1 using 1-chloro-2-nitro-4-[(trifluoromethyl)sulfonyl]benzene (*J. Org. Chem.* 1960, **25**, 60-65) instead of 1-chloro-4-(isopropylsulfonyl)-2-nitrobenzene.

¹H-NMR (CDCl₃) δ:8.86 (d, J= 2.3 Hz, 1H), 8.74 (br s, 1H), 7.92-7.88(m, 1H), 7.01 (d, J= 9.2 Hz, 1H), 3.27 (dd, J= 7.1, 4.9 Hz, 2H), 1.30-1.15 (m, 1H), 1.30-1.15 (m, 1H), 0.75-0.70 (m, 2H), 0.41-0.35 (m, 2H) .
MS (ESI) 323 (M - H)⁻.

35 Step B. 2-Amino-1-(N-cyclopropylmethylamino)-4-[(trifluoromethyl)sulfonyl]benzene

The title compound was prepared according to the procedure described in Step E of Example 1 using N-(cyclopropylmethyl)-2-nitro-4-[(trifluoromethyl)sulfonyl]aniline instead of

N-(cyclopropylmethyl)-4-(isopropylsulfonyl)-2-nitroaniline.

¹H-NMR (CDCl₃) δ:7.54-7.50 (m, 1H), 7.27-7.25 (m, 1H), 6.66 (d, J= 8.6 Hz, 1H), 4.54 (br s, 1H), 3.39 (br s, 2H), 3.09-3.05 (m, 2H), 1.22-1.09 (m, 1H), 0.68-0.59 (m, 2H), 0.34-0.27 (m, 2H).

MS (ESI) 295 (M + H)⁺, 293 (M - H).

5 **Step C. 1-(Cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-[(trifluoromethyl)sulfonyl]- 1*H*-benzimidazole**

The title compound was prepared according to the procedure described in step F of Example 1 using 2-amino-1-(*N*-cyclopropylmethylamino)- 4-[(trifluoromethyl)sulfonyl]benzene (Step B) instead of 2-amino-1-(*N*-cyclopropylmethylamino)-4-(isopropylsulfonyl)benzene.

¹H-NMR (CDCl₃) δ:8.46 (br, 1H), 7.90-7.88 (m, 1H), 7.56 (d, J= 8.6 Hz, 1H), 4.14 (d, J= 6.6 Hz, 2H), 2.87

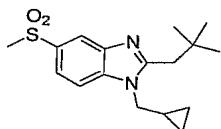
10 (s, 2H), 1.22-1.07 (m, 10H), 0.70-0.64 (m, 2H), 0.44-0.39 (m, 2H).

MS (ESI) 375 (M + H)⁺.

Example 4

1-(Cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-(methylsulfonyl)-1*H*-benzimidazole and its

15 **hydrochloride salt**



Step A. *N*-(Cyclopropylmethyl)-4-(methylsulfonyl)-2-nitroaniline

The title compound was prepared according to the procedure described in Step D of Example 1 using 1-fluoro-4-(methylsulfonyl)-2-nitrobenzene (Acros Organics) instead of 20 1-chloro-4-(isopropylsulfonyl)-2-nitrobenzene.

¹H-NMR (CDCl₃) δ:8.78 (d, J= 2.2 Hz, 1H), 8.51 (br s, 1H), 7.89 (dd J= 9.2, 2.2 Hz, 1H), 6.95 (d, J= 9.2 Hz, 1H), 3.26-3.21 (m, 2H), 3.06 (s, 3H), 1.29-1.16 (m, 1H), 0.74-0.67 (m, 2H), 0.39-0.34 (m, 2H).

Step B. 2-Amino-1-(*N*-cyclopropylmethylamino)-4-(methylsulfonyl)benzene

The title compound was prepared according to the procedure described in Step E of Example 1 25 using *N*-(cyclopropylmethyl)-4-(methylsulfonyl)-2-nitroaniline (Step A) instead of *N*-(cyclopropylmethyl)-4-(isopropylsulfonyl)-2-nitroaniline.

¹H-NMR (CDCl₃) δ:7.40 (dd, J= 8.4, 2.1 Hz, 1H), 7.23 (d, J= 2.1 Hz, 1H), 6.62 (d, J= 8.4 Hz, 1H), 4.11 (br, 1H), 3.43 (br, 2H), 3.05-3.00 (m, 5H), 1.23-1.07 (m, 1H), 0.65-0.58 (m, 2H), 0.31-0.26 (m, 2H).

MS (ESI) 241 (M + H)⁺, 239 (M - H)⁻.

30 **Step C. 1-(Cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-(methylsulfonyl)-1*H*-benzimidazole hydrochloride**

The title compound was prepared according to the procedure described in Step F of Example 1 using 2-amino-1-(*N*-cyclopropylmethylamino)-4-(methylsulfonyl)benzene instead of 2-amino-1-(*N*-cyclopropylmethylamino)-4-(isopropylsulfonyl)benzene. Obtained 35 1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5- (methylsulfonyl)-1*H*-benzimidazole was dissolved in ethyl acetate and to the solution was added 4 N hydrogen chloride in ethyl acetate. Precipitate was collected by filtration to afford the title compound as a white solid.

¹H-NMR (CDCl₃) δ:8.22-8.21 (m, 1H), 8.07 (d, J= 8.6 Hz, 1H), 7.93-7.89 (m, 1H), 4.36 (d, J= 7.0Hz, 2H),

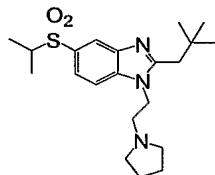
3.28 (s, 3H), 3.01 (s, 2H), 1.33-1.20 (m, 1H), 1.07 (s, 9H), 0.53-0.49 (m, 4H) .

MS (ESI) 321 (M + H)⁺.

m.p. 217 °C

5 Example 5

2-(2,2-Dimethylpropyl)-5-(isopropylsulfonyl)-1-(2-pyrrolidin-1-ylethyl)-1*H*-benzimidazole



Step A. 4-(Isopropylsulfonyl)-2-nitro-N-(2-pyrrolidin-1-ylethyl)aniline

A mixture of 1-chloro-4-(isopropylsulfonyl)-2-nitrobenzene (Step C of Example 1, 200 mg, 0.76 mmol) and 1-(2-aminoethyl)pyrrolidine (0.1 mL, 0.80 mmol) in ethanol (1 mL) was microwaved for 15 min at 130 °C. The reaction was quenched with water and extracted three times with ethyl acetate. The combined organic layers were dried over MgSO₄ and filtered. The filtrate was evaporated under reduced pressure. The residue was crude product as a yellow solid.

LC-MS(ESI) 342. (M+H)⁺.

15 Step B. 2-Amino-4-(isopropylsulfonyl)-1-(N-2-pyrrolidin-1-ylethylamino)benzene

A mixture of crude 4-(isopropylsulfonyl)-2-nitro-N-(2-pyrrolidin-1-ylethyl)aniline (Step A), 10% palladium carbon (20 mg) and acetic acid (0.2 mL) in ethyl acetate (5 mL) was stirred for 2 h at room temperature under H₂ atmosphere then the reaction mixture was filtered. The filtrate was evaporated under reduced pressure. The residue was purified by amine coated silica gel column chromatography (hexane : ethyl acetate = 1 : 2) to give the title compound as an orange solid (122.9 mg, 52%, 2 steps).

¹H-NMR (CDCl₃) δ:7.32 (dd, J= 8.2, 2.0 Hz, 1H), 7.14 (d, J=2.0 Hz, 1H), 6.63 (d, J= 8.2 Hz, 1H), 4.65 (t, J=4.5 Hz, 1H), 3.53 (br, 2H), 3.28-3.22 (m, 2H), 3.12 (m, 1H), 2.83-2.78 (m, 2H), 2.58-2.52 (m, 4H), 1.82-1.77 (m, 4H), 1.27 (d, J=7.0 Hz, 6H).

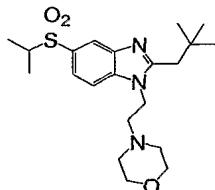
LC-MS (ESI) 312 (M+H)⁺

25 Step C. 2-(2,2-Dimethylpropyl)-5-(isopropylsulfonyl)-1-(2-pyrrolidin-1-ylethyl)-1*H*-benzimidazole

To a solution of 2-amino-4-(isopropylsulfonyl)-1-(N-2-pyrrolidin-1-ylethylamino)benzene (122.9 mg, 0.39 mmol) in ethyl acetate (8 mL) was added *tert*-butylacetyl chloride (60 μL, 0.43 mmol) at room temperature, and the mixture was stirred for 1 h at room temperature. 2N-NaOH (1 mL) and ethanol (3 mL) were then added to the reaction mixture at room temperature, and stirred for 6 h at 80 °C. The reaction was quenched with water, and extracted with three times with ethyl acetate. The combined organic layers were dried over MgSO₄ and filtered. The filtrate was evaporated under reduced pressure. The residue was purified by amine coated silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to give the title compound as an orange solid (107.9 mg, 70%).

¹H-NMR (CDCl₃) δ:8.27 (d, J= 1.6 Hz, 1H), 7.75 (dd, J= 8.5, 1.6 Hz, 1H), 7.47 (d, J= 8.5 Hz, 1H), 4.33-4.39 (m, 2H), 3.28-3.20 (m, 1H), 2.86 (s, 2H), 2.86-2.75 (m, 2H), 2.63-2.55 (m, 4H), 1.85-1.78 (m, 4H), 1.30 (d, J= 6.8 Hz, 6H), 1.12 (s, 9H)

LC-MS (ESI) 392 (M+H)⁺

Example 6**2-(2,2-Dimethylpropyl)-5-(isopropylsulfonyl)-1-(2-morpholin-4-ylethyl)-1H-benzimidazole**5 **Step A. 4-(Isopropylsulfonyl)-N-(2-morpholin-4-ylethyl)-2-nitroaniline**

The title compound was prepared according to the procedure described in Step A of Example 5 using 4-(2-aminoethyl)morpholine instead of 1-(2-aminoethyl)pyrrolidine.

LC-MS (ESI) 358 (M+H)⁺

Step B. 2-Amino-4-(isopropylsulfonyl)-1-(N-2-morpholin-4-ylethylamino)benzene

10 The title compound was prepared according to the procedure described in Step B of Example 5 using 4-(isopropylsulfonyl)-N-(2-morpholin-4-ylethyl)-2-nitroaniline (Step A) instead of 4-(isopropylsulfonyl)-2-nitro-N-(2-pyrrolidin-1-ylethyl)aniline.

¹H-NMR (CDCl₃) δ:7.31 (dd, J= 8.4, 2.0 Hz, 1H), 7.16 (d, J= 2.0 Hz, 1H), 6.62 (d, J= 8.4 Hz, 1H), 4.75-4.67 (m, 1H), 3.73 (br, 4H), 3.57 (br, 2H), 3.26-3.21 (m, 2H), 3.12 (m, J= 6.8 Hz, 1H), 2.73-2.69 (m, 2H), 2.50 (br, 4H), 1.26 (d, J= 6.8 Hz, 6H).

LC-MS (ESI) 328 (M+H)⁺

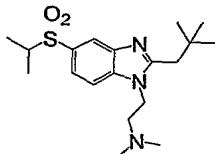
Step C. 2-(2,2-Dimethylpropyl)-5-(isopropylsulfonyl)-1-(2-morpholin-4-ylethyl)-1H-benzimidazole

The title compound was prepared according to the procedure described in Step C of Example 5 using 2-amino-4-(isopropylsulfonyl)-1-(N-2-morpholin-4-ylethylamino)benzene (Step B) instead of 2-amino-4-(isopropylsulfonyl)-1-(N-2-pyrrolidin-1-ylethylamino)benzene.

¹H-NMR (CDCl₃) δ:8.27 (d, J= 1.7 Hz, 1H), 7.76 (dd, J= 8.4, 1.7 Hz, 1H), 7.47 (d, J= 8.4 Hz, 1H), 4.33 (dd, J= 7.0, 6.8 Hz, 2H), 3.68 (dd, J=4.7, 4.4 Hz, 4H), 3.24 (m, J= 7.0 Hz, 1H), 2.87 (s, 2H), 2.68 (dd, J= 7.0, 6.8 Hz, 2H), 2.49 (dd, J= 4.7, 4.4 Hz, 4H), 1.31 (d, J= 7.0 Hz, 6H), 1.12 (s, 9H) .

LC-MS (ESI) 408 (M+H)⁺

25 m.p. 151 °C

Example 7**2-[2-(2,2-Dimethylpropyl)-5-(isopropylsulfonyl)-1H-benzimidazol-1-yl]-N,N-dimethylethanamine**30 **Step A. N-[4-(Isopropylsulfonyl)-2-nitrophenyl]-N',N'-dimethylethane-1,2-diamine**

The title compound was prepared according to the procedure described in Step A of Example 5 using N,N'-dimethylethylenediamine instead of 1-(2-aminoethyl)pyrrolidine.

LC-MS (ESI) 316 (M+H)⁺

Step B. N-[2-(Dimethylamino)ethyl]-4-(isopropylsulfonyl)benzene-1,2-diamine

The title compound was prepared according to the procedure described in Step B of Example 5 using *N*'-[4-(isopropylsulfonyl)-2-nitrophenyl]-*N,N*-dimethylethane-1,2-diamine (Step A) instead of 4-(isopropylsulfonyl)-2-nitro-*N*-(2-pyrrolidin-1-ylethyl)aniline.

5 ¹H-NMR (CDCl₃) δ:7.31 (dd, J= 8.4, 2.0 Hz, 1H), 7.14 (d, J= 2.0 Hz, 1H), 6.62 (d, J= 8.4 Hz, 1H), 4.66 (t, J= 4.3 Hz, 1H), 3.60 (br, 2H), 3.24-3.18 (m, 2H), 3.12 (m, J= 7.0 Hz, 1H), 2.64-2.60 (m, 2H), 2.26 (s, 6H), 1.26 (d, J= 7.0 Hz, 6H).

LC-MS (ESI) 286 (M+H)⁺

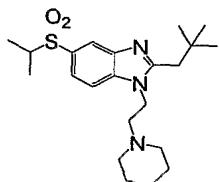
Step C. 2-[2-(2,2-Dimethylpropyl)-5-(isopropylsulfonyl)-1*H*-benzimidazol-1-yl]-*N,N*-dimethylethanamine

10 The title compound was prepared according to the procedure described in Step C of Example 5 using *N*'-[2-(dimethylamino)ethyl]-4-(isopropylsulfonyl)benzene-1,2-diamine (Step B) instead of 2-amino-4-(isopropylsulfonyl)-1-(*N*-2-pyrrolidine-1-yl ethylamino)benzene.

15 ¹H-NMR (CDCl₃) δ:8.27 (d, J= 1.7 Hz, 1H), 7.75 (dd, J= 8.4, 1.7 Hz, 1H), 7.47 (d, J= 8.4 Hz, 1H), 4.31 (br, 2H), 3.23 (m, J= 6.8 Hz, 1H), 2.85 (s, 2H), 2.62 (br, 2H), 2.33 (s, 6H), 1.31 (d, J= 6.8 Hz, 6H), 1.12 (s, 9H).

LC-MS (ESI) 366 (M+H)⁺

m.p. 116 °C

20 **Example 8**2-(2,2-Dimethylpropyl)-5-(isopropylsulfonyl)-1-(2-piperidin-4-ylethyl)-1*H*-benzimidazoleStep A. 4-(Isopropylsulfonyl)-2-nitro-*N*-(2-piperidin-1-ylethyl)aniline

25 The title compound was prepared according to the procedure described in Step A of Example 5 using 1-(2-aminoethyl)piperidine instead of 1-(2-aminoethyl)pyrrolidine.

LC-MS (ESI) 356 (M+H)⁺, 354 (M-H)⁺

Step B. 2-Amino-4-(isopropylsulfonyl)-1-(*N*-2-piperidin-1-ylethylamino)benzene

30 The title compound was prepared according to the procedure described in Step B of Example 5 using 4-(isopropylsulfonyl)-2-nitro-*N*-(2-piperidin-1-ylethyl)aniline (Step A) instead of 4-(isopropylsulfonyl)-2-nitro-*N*-(2-pyrrolidin-1-ylethyl)aniline.

1H-NMR (CDCl₃) δ:7.30 (dd, J= 8.4, 2.1 Hz, 1H), 7.14 (d, J= 2.1 Hz, 1H), 6.61 (d, J= 8.4 Hz, 1H), 3.54 (br, 2H), 3.24-3.17 (m, 2H), 2.67-2.63 (m, 2H), 2.43 (br, 4H), 1.63-1.39 (m, 6H), 1.27 (d, J= 6.8 Hz, 6H).

LC-MS (ESI) 326 (M+H)⁺, 324 (M-H)⁺

Step C. 2-(2,2-Dimethylpropyl)-5-(isopropylsulfonyl)-1-(2-piperidin-1-ylethyl)-1*H*-benzimidazole

35 The title compound was prepared according to the procedure described in Step C of Example 5 using 2-amino-4-(isopropylsulfonyl)-1-(*N*-2-piperidin-1-ylethylamino)benzene (Step B) instead of

2-amino-4-(isopropylsulfonyl)-1-(N-2-pyrrolidine-1-yl ethylamino)benzene.

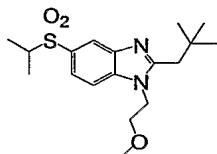
¹H-NMR (CDCl₃) δ:8.27 (d, J= 1.7 Hz, 1H), 7.75 (dd, J= 8.6, 1.7 Hz, 1H), 7.47 (d, J= 8.6 Hz, 1H), 4.32 (dd, J= 7.3, 6.9 Hz, 2H), 3.23 (sep, J= 6.9 Hz, 1H), 2.86 (s, 2H), 2.62 (dd, J= 7.3, 6.9 Hz, 2H), 2.47-2.42 (m, 4H), 1.62-1.54 (m, 4H), 1.50-1.41 (m, 2H), 1.31 (d, J= 6.9 Hz, 6H), 1.12 (s, 9H).

5 LC-MS (ESI) 406 (M+H)⁺

m.p. 139 °C

Example 9

2-(2,2-Dimethylpropyl)-5-(isopropylsulfonyl)-1-(2-methoxyethyl)-1*H*-benzimidazole



10

Step A. 4-(Isopropylsulfonyl)-N-(2-methoxyethyl)-2-nitroaniline

The title compound was prepared according to the procedure described in Step A of Example 5 using 1-(2-aminoethyl)pyrrolidine instead of 1-(2-aminoethyl)pyrrolidine.

LC-MS (ESI) 301 (M+H)⁺

15 Step B. 2-Amino-4-(isopropylsulfonyl)-1-(N-2-methoxyethylamino)benzene

The title compound was prepared according to the procedure described in Step B of Example 5 using 4-(isopropylsulfonyl)-N-(2-methoxyethyl)-2-nitroaniline (Step A) instead of 4-(isopropylsulfonyl)-2-nitro-N-(2-pyrrolidin-1-ylethyl)aniline.

¹H-NMR (CDCl₃) δ:7.33 (dd, J= 8.2, 2.1 Hz, 1H), 7.16 (d, J= 2.1 Hz, 1H), 6.66 (d, J= 8.2 Hz, 1H),

20 3.70-3.66 (m, 2H), 3.41 (s, 3H), 3.35 (br, 2H), 3.12 (m, J= 6.9 Hz, 1H), 1.27 (d, J= 6.9 Hz, 6H)

LC-MS (ESI) 273 (M+H)⁺, 271 (M-H)⁺

Step C. 2-(2,2-Dimethylpropyl)-5-(isopropylsulfonyl)-1-(2-methoxyethyl)-1*H*-benzimidazole

The title compound was prepared according to the procedure described in Step C of Example 5 using 2-amino-4-(isopropylsulfonyl)-N-(2-methoxyethyl)-2-nitroaniline (Step A) instead of

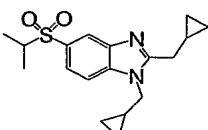
25 2-amino-4-(isopropylsulfonyl)-1-(N-2-pyrrolidin-1-ylethylamino)benzene.

¹H-NMR (CDCl₃) δ:8.28 (d, J= 1.7 Hz, 1H), 7.75 (dd, J= 8.6, 1.7 Hz, 1H), 7.47 (d, J= 8.6 Hz, 1H), 4.40 (dd, J= 5.4 Hz, 2H), 3.67 (dd, J= 5.6, 5.4 Hz, 2H), 3.27 (s, 3H), 3.23 (m, J= 6.8 Hz, 1H), 2.88 (s, 2H), 1.31 (d, J= 6.8 Hz, 6H), 1.11 (s, 9H).

LC-MS (ESI) 353 (M+H)⁺

30 **Example 10**

1,2-bis(Cyclopropylmethyl)-5-(isopropylsulfonyl)-1*H*-benzimidazole



Step A. Cyclopropylacetyl chloride

A mixture of cyclopropylacetic acid (100 mg) and thionyl chloride (1 mL) was stirred for 2 h at

80 °C, then the reaction mixture was cooled and evaporated under reduced pressure. The residue was crude title compound.

Step B. 1,2-bis(Cyclopropylmethyl)-5-(isopropylsulfonyl)-1H-benzimidazole

The title compound was prepared according to the procedure described in Step C of Example 5

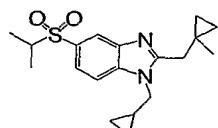
5 from cyclopropylacetyl chloride (Step A) and 2-amino-1-(N-cyclopropylmethylamino)-4-(isopropylsulfonyl)benzene (Step E of Example 1).

¹H-NMR (CDCl₃) δ: 8.30 (br, 1H), 7.77 (br, 1H), 7.47 (d, J= 8.6 Hz, 1H), 4.09 (d, J= 6.6 Hz, 2H), 3.23 (m, J= 6.8 Hz, 1H), 2.89 (d, J= 6.6 Hz, 2H), 1.30 (d, J= 6.8 Hz, 6H), 1.39-1.18 (m, 2H), 0.72-0.63 (m, 4H), 0.44-0.32 (m, 4H).

10 LC-MS (ESI) 333 (M+H)⁺
m.p. 107 °C

Example 11

2-(1-Methylcyclopropylmethyl)-1-(cyclopropylmethyl)-5-(isopropylsulfonyl)-1H-benzimidazole



15

Step A. 1-(Chloromethyl)-1-methylcyclopropane

To a solution of (1-methylcyclopropyl)methanol (500 mg, 5.8 mmol) in dichloromethane (25 mL) was added thionyl chloride (0.5 mL, 6.96 mmol) at -78 °C, and stirred for 1 h at that temperature. The reaction was quenched with saturated NaHCO₃ aq., and the mixture was extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over Na₂SO₄ and filtered. The filtrate was evaporated under reduced pressure. The residue was crude title compound as a colorless oil.

Step B. (1-Methylcyclopropyl)acetonitrile

A mixture of 1-(chloromethyl)-1-methylcyclopropane (Step A) and potassium cyanide in dimethylsulfoxide was stirred for 1 day at 80 °C. The reaction was quenched with water and 2N NaOH, and extracted three times with ether. The combined organic layers were washed with brine, dried over Na₂SO₄ and filtered. The filtrate was evaporated under reduced pressure. The residue was crude title compound as a colorless oil.

Step C. (1-Methylcyclopropyl)acetic acid

30 A mixture of (1-methylcyclopropyl)acetonitrile (Step B, 256 mg, 2.7 mmol) and NaOH (1.08 g) in water was refluxed for 1 day. The reaction was quenched with 2N-HCl to pH3~5. The mixture was extracted three times with ether. The combined organic layers were washed with brine, dried over Na₂SO₄ and filtered. The filtrate was evaporated under reduced pressure. The residue was crude title compound.

¹H-NMR (CDCl₃) δ: 2.26 (s, 2H), 1.16 (s, 3H), 0.49-0.37 (m, 4H).

35 Step D. (1-Methylcyclopropyl)acetyl chloride

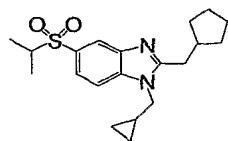
The title compound was prepared according to the procedure described in Step A of Example 10 using (1-methylcyclopropyl)acetic acid (Step C) instead of cyclopropylacetic acid.

Step E. 1-(1-Methylcyclopropylmethyl)-5-(isopropylsulfonyl)-2-[1-methylcyclopropylmethyl]-

1H-benzimidazole

The title compound was prepared according to the procedure described in Step C of Example 5 from (1-methylcyclopropyl)acetyl chloride (Step D) and 2-amino-1-(*N*-cyclopropylmethylamino)-4-(isopropylsulfonyl)benzene (Step E of Example 1).

- 5 $^1\text{H-NMR}$ (CDCl_3) δ : 8.31 (d, J = 1.7 Hz, 1H), 7.77 (dd, J = 8.4, 1.7 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 4.12 (d, J = 6.8 Hz, 2H), 3.24 (m, J = 7.0 Hz, 1H), 2.99 (s, 2H), 1.36-1.19 (m, 1H), 1.32 (d, J = 7.0 Hz, 6H), 1.19 (s, 3H), 0.70-0.39 (m, 8H).
 LC-MS (ESI) 347 ($M+\text{H}^+$)⁺

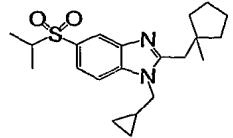
10 Example 12**2-(Cyclopentylmethyl)-1-(cyclopropylmethyl)-5-(isopropylsulfonyl)-1H-benzimidazole****Step A. Cyclopentylacetyl chloride**

- 15 The title compound was prepared according to the procedure described in Step A of Example 10 using cyclopentylacetic acid instead of cyclopropylacetic acid.

Step B. 2-(Cyclopentylmethyl)-1-(cyclopropylmethyl)-5-(isopropylsulfonyl)-1H-benzimidazole

- The title compound was prepared according to the procedure described in Step C of Example 5 from cyclopentylacetyl chloride (Step B) and 2-amino-1-(*N*-cyclopropylmethylamino)-4-(isopropylsulfonyl)benzene (Step E of Example 1).
 20 $^1\text{H-NMR}$ (CDCl_3) δ : 8.27 (d, J = 1.7 Hz, 1H), 7.75 (dd, J = 8.4, 1.7 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 4.08 (d, J = 6.6 Hz, 2H), 3.23 (m, J = 6.9 Hz, 1H), 2.93 (d, J = 7.4 Hz, 2H), 2.60-2.48 (m, 1H), 1.98-1.86 (m, 2H), 1.76-1.56 (m, 4H), 1.30 (d, J = 6.8 Hz, 6H), 1.38-1.17 (m, 3H), 0.70-0.62 (m, 2H), 0.44-0.39 (m, 2H).
 LC-MS (ESI) 361 ($M+\text{H}^+$)⁺
 m.p. 137 °C

25

Example 13**1-(Cyclopropylmethyl)-2-(1-methylcyclopentylmethyl)-5-(isopropylsulfonyl)-1H-benzimidazole****Step A. (1-Methylcyclopentyl)acetyl chloride**

- 30 The title compound was prepared according to the procedure described in Step A of Example 10 using (1-methylcyclopentyl)acetic acid (Chem. Ber. 100, 978-983, 1967) instead of cyclopropylacetic acid.

Step B. 1-(Cyclopropylmethyl)-2-(1-methylcyclopentylmethyl)-5-(isopropylsulfonyl)-1H-benzimidazole

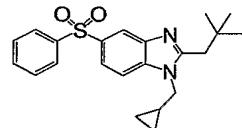
- The title compound was prepared according to the procedure described in Step C of Example 5 from (1-methylcyclopentyl)acetyl chloride (Step A) and 2-amino-1-(*N*-cyclopropylmethylamino)-4-(isopropylsulfonyl)benzene (Step E of Example 1).

¹H-NMR (CDCl₃) δ:8.28 (d, *J*= 1.6 Hz, 1H), 7.75 (dd, *J*= 8.4, 1.6 Hz, 1H), 7.47 (d, *J*= 8.4 Hz, 1H), 4.12 (d, *J*= 6.4 Hz, 2H), 3.24 (m, *J*= 6.9 Hz, 1H), 2.96 (s, 2H), 1.81-1.62 (m, 6H), 1.58-1.44 (m, 2H), 1.31 (d, *J*= 6.9 Hz, 6H), 1.33-1.15 (m, 1H), 1.09 (s, 3H), 0.68-0.61 (m, 2H), 0.43-0.37 (m, 2H).
LC-MS (ESI) 375 (M+H)⁺

5 m.p. 122 °C

Example 14

1-(Cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-(phenylsulfonyl)-1*H*-benzimidazole



10 Step A. (Cyclopropylmethyl)[2-nitro-4-(phenylsulfonyl)phenyl]amine

The title compound was prepared according to the procedure described in Step A of Example 5 from 1-chloro-2-nitro-4-(phenylsulfonyl)benzene (J. Chem. Soc. Perkin Trans. 1, 1988, 991-998) and cyclopropylmethylamine.

LC-MS (ESI) 333 (M+1)⁺

15 Step B. 2-Amino-1-(*N*-cyclopropylmethylamino)-4-(phenylsulfonyl)benzene

The title compound was prepared according to the procedure described in Step B of Example 5 using (cyclopropylmethyl)[2-nitro-4-(phenylsulfonyl)phenyl]amine (Step A) instead of 4-(isopropylsulfonyl)-2-nitro-*N*-(2-pyrrolidin-1-ylethyl)aniline.

16 ¹H-NMR (CDCl₃) δ:7.92-7.86 (m, 2H), 7.53-7.41 (m, 4H), 7.24 (d, *J*= 2.1 Hz, 1H), 6.58 (d, *J*= 8.4 Hz, 1H), 2.98 (d, *J*= 6.9 Hz, 1H), 1.20-1.04 (m, 1H), 0.61-0.55 (m, 2H), 0.28-0.22 (m, 2H).

LC-MS (ESI) 303 (M+H)⁺, 301 (M-H)⁺

Step C. 1-(Cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-(phenylsulfonyl)-1*H*-benzimidazole

The title compound was prepared according to the procedure described in Step C of Example 5 using 2-amino-1-(*N*-cyclopropylmethylamino)-4-(phenylsulfonyl)benzene (Step B) instead of 2-amino-4-(isopropylsulfonyl)-1-(*N*-2-pyrrolidine-1-yl ethylamino)benzene.

17 ¹H-NMR (CDCl₃) δ:8.35-8.34 (m, 1H), 8.00-7.97 (m, 2H), 7.86-7.82 (m, 1H), 7.55-7.41 (m, 4H), 4.08 (d, *J*= 6.6 Hz, 2H), 2.81 (s, 2H), 1.18-1.08 (m, 1H), 1.08 (s, 9H), 0.64-0.56 (m, 2H), 0.39-0.33 (m, 2H).

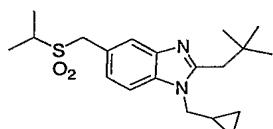
LC-MS(ESI) 383 (M+H)⁺.

m.p. 173 °C

30

Example 15

1-(Cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-[*(isopropylsulfonyl)methyl*]-1*H*-benzimidazole and its hydrochloride salt



35 Step A. Methyl 4-[(cyclopropylmethyl)amino]-3-nitrobenoate

The title compound was prepared according to the procedure described in Step D of Example 1 using methyl 4-chloro-3-nitrobenzoate (Lancaster Synthesis Ltd.) instead of 1-chloro-4-(isopropylsulfonyl)-2-nitrobenzene.

¹H-NMR (CDCl₃) δ:8.90 (d, J= 2.0 Hz, 1H), 8.43 (br s, 1H), 8.04 (dd J= 9.1, 2.0 Hz, 1H), 6.84 (d, J= 9.1 Hz, 1H), 3.90 (s, 3H), 3.22(dd, J= 7.0, 4.9 Hz, 2H), 1.26-1.13 (m, 1H), 0.72-0.65 (m, 2H), 0.38-0.32 (m, 2H).

MS (ESI) 251 (M + H)⁺.

Step B. Methyl 3-amino-4-[(cyclopropylmethyl)amino]benzoate

The title compound was prepared according to the procedure described in Step E of Example 1 using methyl 4-[(cyclopropylmethyl)amino]-3-nitrobenzoate (Step A) instead of N-(cyclopropylmethyl)-4-(isopropylsulfonyl)-2-nitroaniline.

¹H-NMR (CDCl₃) δ:7.58 (dd, J= 8.4, 2.0 Hz, 1H), 7.41 (d, J= 2.0 Hz, 1H), 6.57 (d, J= 8.4 Hz, 1H), 4.06 (br s, 1H), 3.85 (s, 3H), 3.29 (br s, 2H), 3.04-3.00 (m, 2H), 1.20-1.09 (m, 1H), 0.63-0.56 (m, 2H), 0.31-0.25 (m, 2H).

MS (ESI) 221 (M + H)⁺.

Step C. Methyl 1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazole -5-carboxylate

The title compound was prepared according to the procedure described in Step F of Example 1 using methyl 3-amino-4-[(cyclopropylmethyl)amino]benzoate (Step B) instead of 2-amino-1-(N-cyclopropylmethylamino)-4-(isopropylsulfonyl)benzene.

¹H-NMR (CDCl₃) δ:8.47-8.46 (m, 1H), 7.97 (dd, J= 8.6, 1.5 Hz, 1H), 7.37 (d, J= 8.6 Hz, 1H), 4.10 (d, J=7.1 Hz, 2H), 3.94 (s, 3H), 2.83 (s, 2H), 1.29-1.19 (m, 1H), 1.09 (s, 9H), 0.65-0.57 (m, 2H), 0.41-0.35 (m, 2H).

MS (ESI) 301 (M + H)⁺.

Step D. [1-(Cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazol-5-yl] methanol

To a suspension of lithium aluminum hydride (391mg, 8.3 mmol) in tetrahydrofuran (15 mL) was added a tetrahydrofuran solution of methyl 1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazole-5-carboxylate (Step C, 990 mg, 3.3 mmol) at 0 °C. The mixture was stirred at 0 °C for 3 h. The mixture was quenched with potassium fluoride and sodium sulfate decahydrate and filtered. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 1 : 2 as eluent) to afford the title compound (573 mg, 64%) as red gum.

¹H-NMR (CDCl₃) δ:7.71 (s, 1H), 7.36-7.30 (m, 2H), 4.78 (s, 2H), 4.07 (d, J= 6.4 Hz, 2H), 2.81 (s, 2H), 1.23-1.10 (m, 1H), 1.07 (s, 9H), 0.61-0.55 (m, 2H), 0.39-0.34 (m, 2H), a peak of OH was not observed.

MS (ESI) 273 (M + H)⁺.

Step E. 5-(Chloromethyl)-1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*- benzimidazole

To a solution of [1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*- benzimidazol-5-yl]methanol (Step D, 200 mg, 0.73 mmol) in dichloromethane (3 mL) were added methanesulfonyl chloride (114 μL, 1.5 mmol) and triethylamine (226 μL, 1.6 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h and at room temperature for 2 h. Water (2 mL) was added and the mixture was extracted with ethyl acetate (10 mM x 2). The organic extracts were dried over sodium sulfate and concentrated to afford the title

compound as pale red oil.

¹H-NMR (CDCl₃) δ:7.82 (br s, 1H), 7.41-7.32 (m, 2H), 4.75 (s, 2H), 4.09 (d, J= 5.7 Hz, 2H), 2.88 (s, 2H), 1.23-1.14 (m, 1H), 1.09 (s, 9H), 0.68-0.58 (m, 2H), 0.41-0.36 (m, 2H) .

MS (ESI) 291 (M + H)⁺.

5 **Step F. 1-(Cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-[(isopropylthio)methyl]-1*H*-benzimidazole**

To a suspension of sodium hydride (washed with hexane, 30 mg, 1.3 mmol) in N,N-dimethylformamide (2 mL) was added 2-propanethiol (117 μL, 1.3 mmol) at 0 °C. After stirring for 30 min, a N,N-dimethylformamide solution of 5-(chloromethyl)-1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazole (Step E) was added and the mixture was stirred at 100 °C for 17.5 h. Water (5 mL) was added and the mixture was extracted with ethyl acetate (15 mL x 2) and washed with brine (5 mL). The organic extracts were dried over sodium sulfate and concentrated. The residue was purified by pTLC (hexane : ethyl acetate = 3 : 1) to give the title compound (74 mg, 67% over 2 steps) as pale brown oil.

¹H-NMR (CDCl₃) δ:7.65 (br s, 1H), 7.32-7.23 (m, 2H), 4.05 (d, J= 6.6 Hz, 2H), 3.87 (s, 2H), 2.88-2.82 (m, 1H), 2.80 (s, 2H), 1.26 (d, J= 6.8 Hz, 6H), 1.24-1.13 (m, 1H), 1.08 (s, 9H), 0.62-0.56 (m, 2H), 0.39-0.34 (m, 2H).

MS (ESI) 331 (M + H)⁺.

Step G. 1-(Cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-[(isopropylsulfonyl)methyl]-1*H*-benzimidazole hydrochloride

20 The title compound was prepared according to the procedure described in Step B of Example 1 using 1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-[(isopropylthio)methyl]-1*H*-benzimidazole(Step F) instead of 1-chloro-4-(isopropylthio)benzene. Obtained 1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-[(isopropylsulfonyl)methyl]-1*H*-benzimidazole was dissolved in ethyl acetate and to the solution was added 4 N hydrogen chloride in ethyl acetate. The precipitate was collected by filtration to afford the title compound as a white solid.

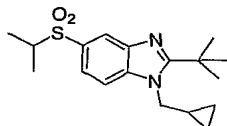
¹H-NMR (CDCl₃) δ:8.11 (br s, 1H), 7.74-7.71 (m, 1H), 7.65-7.63 (m, 1H), 4.37 (s, 2H), 4.23 (d, J= 6.8 Hz, 2H), 3.21 (2, 2H), 3.15-3.06 (m, 1H), 1.44 (d, J= 6.8 Hz, 6H), 1.33-1.21 (m, 1H), 1.18 (s, 9H), 0.80-0.73 (m, 2H), 0.50-0.45 (m, 2H).

MS (ESI) 363 (M + H)⁺.

30

Example 16

2-*tert*-Butyl-1-(cyclopropylmethyl)-5-(isopropylsulfonyl)-1*H*-benzimidazole and its hydrochloride salt



35 The title compound was prepared according to the procedure described in Step F of Example 1 using pivaloyl chloride instead of *tert*-butylacetyl chloride.

Obtained 2-*tert*-butyl-1-(cyclopropylmethyl)-5-(isopropylsulfonyl)-1*H*-benzimidazole was dissolved in ethyl acetate and to the solution was added 4 N hydrogen chloride in ethyl acetate. The

precipitate was collected by filtration to afford the title compound as a white solid.

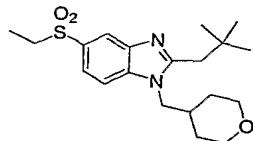
¹H-NMR (CDCl₃) δ: 8.77-8.69 (m, 1H), 7.84-7.72 (m, 2H), 4.52 (d, J= 6.6 Hz, 2H), 3.29-3.16 (m, 1H), 1.82 (s, 9H), 1.26-1.23 (m, 7H), 0.88-0.81 (m, 2H), 0.67-0.61 (m, 2H).

MS (ESI) 335 (M + H)⁺

5

Example 17

2-(2,2-Dimethylpropyl)-5-(ethylsulfonyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole



10 Step A. 4-(Ethylsulfonyl)-2-nitro-N-(tetrahydro-2H-pyran-4-ylmethyl)aniline

The title compound was prepared according to the procedure described in Step A of Example 5 from 1-chloro-4-(ethylsulfonyl)-2-nitrobenzene (Step C of Example 2) and 4-aminomethyltetrahydropyran (Apollo Scientific Ltd.).

ESI-MS 329 (M+H)⁺, 327 (M-H)

15 Step B. 4-(Ethylsulfonyl)-N¹-(tetrahydro-2H-pyran-4-ylmethyl)benzene-1,2-diamine

The title compound was prepared according to the procedure described in Step E of Example 1 using 4-(ethylsulfonyl)-2-nitro-N-(tetrahydro-2H-pyran-4-ylmethyl)aniline (Step A) instead of N-(cyclopropylmethyl)-4-(isopropylsulfonyl)-2-nitroaniline.

ESI-MS 299 (M+H)⁺, 297 (M-H)

20 Step C. 2-(2,2-Dimethylpropyl)-5-(ethylsulfonyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole

To a solution of 4-(ethylsulfonyl)-N¹-(tetrahydro-2H-pyran-4-ylmethyl)benzene-1,2-diamine (Step B) in ethyl acetate (16 mL) was added *tert*-butylacetyl chloride (0.1 mL, 0.8 mmol) at room temperature. After stirring for 2 h, the mixture was quenched with water and extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate and filtered. The filtrate was evaporated under reduced pressure. The residue was dissolved in ethanol and 2N sodium hydroxide solution. The mixture was microwaved for 30 min at 130 °C. The reaction mixture was quenched with water and extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate and filtered. The filtrate was evaporated under reduced pressure. The residue was purified by amine coated silica gel column chromatography (hexane : ethyl acetate = 2 : 1 as eluent) to afford the title compound (103 mg, 34%) as a white solid.

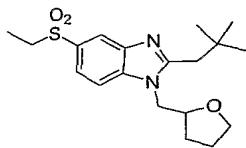
¹H-NMR (CDCl₃) δ: 8.31 (d, J= 2.0 Hz, 1H), 7.80 (dd, J= 8.6, 2.0 Hz, 1H), 7.44 (d, J= 8.6 Hz, 1H), 4.11 (d, J= 7.3 Hz, 2H), 4.02-3.93 (m, 2H), 3.35-3.25 (m, 2H), 3.17 (q, J= 7.3 Hz, 2H), 2.84 (s, 2H), 2.15-2.02 (m, 1H), 1.49-1.39 (m, 4H), 1.30 (t, J= 7.3 Hz, 3H), 1.10 (s, 9H).

ESI-MS 379 (M+H)⁺

35

Example 18

2-(2,2-Dimethylpropyl)-5-(ethylsulfonyl)-1-(tetrahydrofuran-2-ylmethyl)-1H-benzimidazole

Step A. 4-(Ethylsulfonyl)-2-nitro-N-(tetrahydrofuran-2-ylmethyl)aniline

The title compound was prepared according to the procedure described in Step A of Example 5

5 from 1-chloro-4-(ethylsulfonyl)-2-nitrobenzene (Step C of Example 2) and 1-(tetrahydrofuran-2-yl)methanamine (tetrahydrofurfurylamine available from Acros Organics).

ESI-MS 315 ($M+H$)⁺, 313 ($M-H$)⁻

Step B. 4-(Ethylsulfonyl)-N¹-(tetrahydrofuran-2-ylmethyl)benzene-1,2-diamine

The title compound was prepared according to the procedure described in Step E of Example 1

10 using 4-(ethylsulfonyl)-2-nitro-N-(tetrahydrofuran-2-ylmethyl)aniline (Step A) instead of *N*-(cyclopropylmethyl)-4-(isopropylsulfonyl)-2-nitroaniline.

ESI-MS 285 ($M+H$)⁺

Step C. 2-(2,2-Dimethylpropyl)-5-(ethylsulfonyl)-1-(tetrahydrofuran-2-ylmethyl)-1*H*-benzimidazole

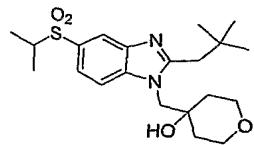
The title compound was prepared according to the procedure described in Step C of Example

15 17 using 4-(ethylsulfonyl)-N¹-(tetrahydrofuran-2-ylmethyl)benzene-1,2-diamine (Step B) instead of 4-(ethylsulfonyl)-N¹-(tetrahydro-2*H*-pyran-4-ylmethyl)benzene-1,2-diamine.

1*H*-NMR ($CDCl_3$) δ : 8.30 (d, $J=2.0$ Hz, 1H), 7.78 (dd, $J=8.6, 2.0$ Hz, 1H), 7.52 (d, $J=8.6$ Hz, 1H), 4.34-4.28 (m, 2H), 4.42-4.16 (m, 1H), 3.86-3.68 (m, 2H), 3.16 (q, $J=7.2$ Hz, 2H), 2.9 (s, 2H), 2.10-1.81 (m, 4H), 1.29 (t, $J=7.9$ Hz, 3H), 1.10 (s, 9H).

20 ESI-MS 365 ($M+H$)⁺

m.p. 142 °C

Example 194-[2-(2,2-Dimethylpropyl)-5-(isopropylsulfonyl)-1*H*-benzimidazol-1-yl]methyl]tetrahydro-2*H*-pyran-4-olStep A. 4-(Aminomethyl)tetrahydro-2*H*-pyran-4-ol hydrochloride

To a mixture of trimethylsilyl cyanide (6.8 mL, 51.0 mmol) and zinc iodide (100 mg, 0.31 mmol)

30 in toluene (50 mL) was added tetrahydro-4*H*-pyran-4-one (5.0 g, 49.9 mmol) at 0 °C. After stirring for 3 h at room temperature, the mixture was added to a suspension of lithium aluminum hydride in tetrahydrofuran at 0 °C. The resulting mixture was stirred for 4 h at room temperature. After cooling to 0 °C, the mixture was quenched with potassium fluoride and sodium sulfate decahydrate and filtered. The filtrate was concentrated and the residue was acidified with 4 N hydrogen chloride in ethyl acetate. 35 After evaporation, obtained precipitate was washed with methanol and collected by filtration to afford the

title compound (4.2 g, 25%).

¹H-NMR (DMSO-d₆) δ:8.06 (br, 3H), 3.61-3.60 (m, 4H), 2.79-2.77 (m, 2H), 1.61-1.47 (m, 4H).

Step B. 4-({[4-(Isopropylsulfonyl)-2-nitrophenyl]amino}methyl)tetrahydro-2H-pyran-4-ol

The title compound was prepared according to the procedure described in Step A of Example 5

5 from 1-chloro-4-(isopropylsulfonyl)-2-nitrobenzene (Step C of Example 1), 4-(aminomethyl)tetrahydro-2H-pyran-4-ol hydrochloride (Step A of Example 19) and triethylamine.

¹H-NMR (CDCl₃) δ:8.75 (br, 1H), 8.68 (d, J= 2.0 Hz, 1H), 7.80 (dd J= 8.6, 2.0 Hz, 1H), 7.04 (d, J= 8.6 Hz, 1H), 3.85-3.79 (m, 4H), 3.40 (d, J= 5.3 Hz, 2H), 3.23-3.13 (m, 1H), 1.84-1.68 (m, 4H), 1.31 (d, J= 6.6 Hz, 6H), a peak of OH was not identified.

10 MS (ESI) 359 (M + H)⁺, 357 (M - H)⁻

Step C. 4-({[2-Amino-4-(isopropylsulfonyl)]amino}methyl)tetrahydro-2H-pyran-4-ol

The title compound was prepared according to the procedure described in Step E of Example 1 using 4-({[4-(isopropylsulfonyl)-2-nitrophenyl]amino}methyl)tetrahydro-2H-pyran-4-ol (Step B) instead of N-(cyclopropylmethyl)-4-(isopropylsulfonyl)-2-nitroaniline.

15 ¹H-NMR (CDCl₃) δ:7.31-7.27 (m, 1H), 7.13 (d, J= 2.0 Hz, 1H), 6.66 (d, J= 8.6 Hz, 1H), 4.39 (br, 1H), 3.84-3.80 (m, 4H), 3.43 (br, 2H), 3.18-3.07 (m, 3H), 1.86-1.67 (m, 4H), 1.26 (d, J= 6.6 Hz, 6H), a peak of OH was not identified.

MS (ESI) 329 (M + H)⁺, 327 (M - H)⁻

Step D. 4-[{2-(2,2-Dimethylpropyl)-5-(isopropylsulfonyl)-1H-benzimidazol-1-yl]methyl}tetrahydro-2H-pyra

20 n-4-ol

The title compound was prepared according to the procedure described in Step F of Example 1 using 4-({[2-amino-4-(isopropylsulfonyl)]amino}methyl)tetrahydro-2H-pyran-4-ol (Step C) instead of 2-amino-1-(N-cyclopropylmethylamino)-4-(isopropylsulfonyl)benzene.

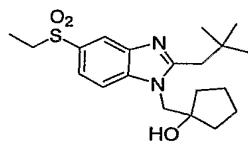
25 ¹H-NMR (CDCl₃) δ:8.27 (d, J= 2.2 Hz, 1H), 7.72 (dd, J= 8.6, 2.2 Hz, 1H), 7.57 (d, J= 8.6 Hz, 1H), 4.24 (s, 2H), 3.88-3.81 (m, 2H), 3.73-3.64 (m, 2H), 3.29-3.19 (m, 1H), 2.92 (s, 2H), 1.95-1.82 (m, 2H), 1.47-1.42 (m, 2H), 1.32 (d, J= 7.3 Hz, 6H), 1.08 (s, 9H), a peak of OH was not identified.

MS (ESI) 409 (M + H)⁺

m.p. 189 °C

30 **Example 20**

1-[{2-(2,2-Dimethylpropyl)-5-(ethylsulfonyl)-1H-benzimidazol-1-yl]methyl}cyclopentanol



Step A. 1-({[4-(Ethylsulfonyl)-2-nitrophenyl]amino}methyl)cyclopentanol

35 The title compound was prepared according to the procedure described in Step A of Example 5 from 1-chloro-4-(ethylsulfonyl)-2-nitrobenzene (Step C of Example 2), 1-(aminomethyl)cyclopentanol hydrochloride (*J. Med. Chem.* 1981, 24, 12-16) and triethylamine.

¹H-NMR (CDCl₃) δ:8.80 (br, 1H), 8.74 (d, J= 2.3 Hz, 1H), 7.85 (dd J= 8.9, 2.3 Hz, 1H), 7.03 (d, J= 8.9 Hz,

1H), 3.47 (d, $J= 5.3$ Hz, 2H), 3.12 (q, $J= 7.3$ Hz, 2H), 1.94-1.74 (m, 8H), 1.30 (t, $J= 7.3$ Hz, 3H), a peak of OH was not identified.

MS (ESI) 329 ($M + H$)⁺, 327 ($M - H$)⁻

Step B. 1-{[2-Amino-4-(ethylsulfonyl)phenyl]amino}methyl)cyclopentanol

5 The title compound was prepared according to the procedure described in Step E of Example 1 using 1-({[4-(ethylsulfonyl)-2-nitrophenyl]amino}methyl)cyclopentanol (Step A) instead of N-(cyclopropylmethyl)-4-(isopropylsulfonyl)-2-nitroaniline.

10 ¹H-NMR (CDCl₃) δ : 7.35 (dd, $J= 8.2, 2.0$ Hz, 1H), 7.18 (d, $J= 2.0$ Hz, 1H), 6.68 (d, $J= 8.2$ Hz, 1H), 4.45-4.40 (m, 1H), 3.50-3.45 (m, 2H), 3.24 (d, $J= 5.9$ Hz, 2H), 3.06 (q, $J= 7.6$ Hz, 2H), 1.95-1.60 (m, 8H), 1.25 (d, $J= 7.6$ Hz, 3H), a peak of OH was not identified.

MS (ESI) 299 ($M + H$)⁺, 297 ($M - H$)⁻

Step C. 1-{[2-(2,2-Dimethylpropyl)-5-(ethylsulfonyl)-1H-benzimidazol-1-yl]methyl)cyclopentanol

15 The title compound was prepared according to the procedure described in Step F of Example 1 using 1-({[2-amino-4-(ethylsulfonyl)phenyl]amino}methyl)cyclopentanol (Step B) instead of 2-amino-1-(N-cyclopropylmethylamino)-4-(isopropylsulfonyl)benzene.

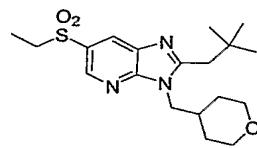
20 ¹H-NMR (CDCl₃) δ : 8.30 (d, $J= 2.0$ Hz, 1H), 7.76 (dd, $J= 8.6, 2.0$ Hz, 1H), 7.58 (d, $J= 8.6$ Hz, 1H), 4.38 (s, 2H), 3.16 (q, $J= 7.3$ Hz, 2H), 2.95 (s, 2H), 1.92-1.63 (m, 8H), 1.30 (t, $J= 7.3$ Hz, 3H), 1.08 (s, 9H), a peak of OH was not identified.

MS (ESI) 379 ($M + H$)⁺

25 m.p. 172 °C

Example 21

2-(2,2-Dimethylpropyl)-6-(ethylsulfonyl)-3-(tetrahydro-2H-pyran-4-ylmethyl)-3H-imidazo[4,5-b]pyridine



25

Step A. 5-(Ethylthio)pyridin-2-amine

To a solution of 5-bromo-2-(2,2,5,5-tetramethyl-1,2,5-azadisilolidin-1-yl)pyridine (4 g, 12.7 mmol, *J. Am. Chem. Soc.* 1997, 119, 5499-5511) in tetrahydrofuran (40 mL) was added *n*-butyllithium at -78 °C under nitrogen. After 2 h, diethyl disulfide (1.7 mL, 12.7 mmol) was added and the mixture was stirred at -78 °C for 3 h. The temperature was gradually raised to room temperature over 2 h. The mixture was poured into ice aqueous sodium hydrogencarbonate. The organic layer was separated and extracted with 2 N hydrochloric acid. The aqueous layer was separated and basified and the mixture was extracted with ethyl acetate (50 mL x 4). The organic extracts were dried over sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 1 : 1 as eluent) to afford the title compound (1.23 g, 63%) as a pale brown solid.

¹H-NMR (CDCl₃) δ : 8.16 (d, $J= 2.5$ Hz, 1H), 7.52 (dd, $J= 8.4, 2.5$ Hz, 1H), 6.46 (d, $J= 8.4$ Hz, 1H), 4.52 (br,

2H), 2.74 (q, $J= 7.3$ Hz, 2H), 1.22 (t, $J= 7.3$ Hz, 3H).

MS (ESI) 155 ($M + H$)⁺

Step B. 5-(Ethylsulfonyl)pyridin-2-amine

To a solution of 5-(ethylthio)pyridin-2-amine (Step A, 1.23 g, 7.96 mmol) in dichloromethane (30

5 mL) were added trifluoroacetic acid (1.2 mL, 15.9 mmol) and m-chloroperbenzoic acid (4.3 g, 17.5 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h. Aqueous sodium sulfite (20 mL) was added. The mixture was extracted with dichloromethane (30 mL x 3) and washed with aqueous sodium hydrogencarbonate (15 mL x 2). The organic extracts were dried over sodium sulfate and concentrated to afford the title compound (1.43 g, 97%) as a white solid.

10 1 H-NMR (CDCl₃) δ: 8.55 (d, $J= 2.3$ Hz, 1H), 7.84 (dd, $J= 8.9, 2.3$ Hz, 1H), 6.56 (d, $J= 8.9$ Hz, 1H), 5.21 (br, 2H), 3.10 (q, $J= 7.3$ Hz, 2H), 1.30 (t, $J= 7.3$ Hz, 3H).

MS (ESI) 187 ($M + H$)⁺, 185 ($M - H$)⁻

Step C. 5-(Ethylsulfonyl)-3-nitropyridin-2-ol

To a solution of 5-(ethylsulfonyl)pyridin-2-amine (Step B, 1.43 g, 7.7 mmol) was added nitric acid

15 (fuming, 3.2 mL, 77 mmol) at 90 °C and the mixture was stirred for 15 min. After cooling to room temperature, the mixture was poured into ice water. The resulting mixture was extracted with ethyl acetate (30 mL x 2). The organic extracts were washed with water (15 mL x 2) and concentrated. The residual solid was washed with methanol and collected by filtration to afford the title compound (575 mg, 32%) as a pale yellow solid.

20 1 H-NMR (DMSO-d6) δ: 8.62 (dd, $J= 2.7, 0.6$ Hz, 1H), 8.35 (dd, $J= 2.7, 0.6$ Hz, 1H), 3.38 (q, $J= 7.3$ Hz, 2H), 1.17 (t, $J= 7.3$ Hz, 3H), a peak of OH was not identified.

MS (ESI) 187 ($M + H$)⁺, 185 ($M - H$)⁻

Step D. 2-Chloro-5-(ethylsulfonyl)-3-nitropyridine

To a solution of 5-(ethylsulfonyl)-3-nitropyridin-2-ol (Step C, 575 mg, 2.5 mmol) in thionyl

25 chloride (7 mL) was added *N,N*-dimethylformamide (one drop). The mixture was stirred under reflux for 2 h and concentrated to afford the crude title compound as a white solid.

1 H-NMR (DMSO-d6) δ: 9.16 (d, $J= 2.2$ Hz, 1H), 8.99 (d, $J= 2.3$ Hz, 1H), 3.55 (q, $J= 7.3$ Hz, 2H), 1.17 (t, $J= 7.3$ Hz, 3H).

Step E. 5-(Ethylsulfonyl)-3-nitro-N-(tetrahydro-2H-pyran-4-ylmethyl)pyridin-2-amine

30 The title compound was prepared according to the procedure described in Step A of Example 5 from 2-chloro-5-(ethylsulfonyl)-3-nitropyridine (Step D) and 4-aminomethyltetrahydropyran (Apollo Scientific Ltd.).

35 1 H-NMR (CDCl₃) δ: 8.86 (d, $J= 2.0$ Hz, 1H), 8.81 (d, $J= 2.0$ Hz, 1H), 8.74 (br 1H), 4.06-4.00 (m, 2H), 3.65 (t, $J= 6.6$ Hz, 2H), 3.46-3.36 (m, 2H), 3.17 (q, $J= 7.6$ Hz, 2H), 2.02-1.90 (m, 1H), 1.74-1.69 (m, 2H), 1.51-1.40 (m, 2H), 1.36 (t, $J= 7.6$ Hz, 3H).

MS (ESI) 330 ($M + H$)⁺, 328 ($M - H$)⁻

Step F. 5-(Ethylsulfonyl)-N²-(tetrahydro-2H-pyran-4-ylmethyl)pyridin-2,3-diamine

The title compound was prepared according to the procedure described in Step E of Example 1 using 5-(ethylsulfonyl)-3-nitro-N-(tetrahydro-2H-pyran-4-ylmethyl)pyridin-2-amine (Step E) instead of 40 N-(cyclopropylmethyl)-4-(isopropylsulfonyl)-2-nitroaniline.

¹H-NMR (CDCl₃) δ: 8.24 (d, J= 2.0 Hz, 1H), 7.22 (d, J= 2.0 Hz, 1H), 4.95 (br 1H), 4.03-3.98 (m, 2H), 3.51-3.36 (m, 4H), 3.28 (br, 2H), 3.08 (q, J= 7.3 Hz, 2H), 2.03-1.87 (m, 1H), 1.73-1.69 (m, 2H), 1.48-1.37 (m, 2H), 1.29 (t, J= 7.3 Hz, 3H).

MS (ESI) 300 (M + H)⁺, 298 (M - H)⁻

- 5 Step G. 2-(2,2-Dimethylpropyl)-6-(ethylsulfonyl)-3-(tetrahydro-2*H*-pyran-4-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine

The title compound was prepared according to the procedure described in Step C of Example 17 using 5-(ethylsulfonyl)-N²-(tetrahydro-2*H*-pyran-4-ylmethyl)pyridin-2,3-diamine (Step F) instead of 4-(ethylsulfonyl)-N¹-(tetrahydro-2*H*-pyran-4-ylmethyl)benzene-1,2-diamine.

- 10 ¹H-NMR (CDCl₃) δ: 8.85 (d, J= 2.3 Hz, 1H), 8.47 (d, J= 2.3 Hz, 1H), 4.24 (d, J= 7.3 Hz, 2H), 4.01-3.93 (m, 2H), 3.36-3.27 (m, 2H), 3.20 (q, J= 7.3 Hz, 2H), 2.87 (s, 2H), 2.35-2.16 (m, 1H), 1.50-1.42 (m, 4H), 1.35 (t, J= 7.3 Hz, 3H), 1.12 (s, 9H).

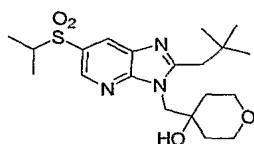
MS (ESI) 380 (M + H)⁺, 378 (M - H)⁻

m.p. 191 °C

15

Example 22

4-[{2-(2,2-Dimethylpropyl)-6-(isopropylsulfonyl)-3*H*-imidazo[4,5-*b*]pyridin-3-yl]methyl}tetrahydro-2*H*-pyran-4-ol



20

Step A. 5-(Isopropylthio)pyridin-2-amine

The title compound was prepared according to the procedure described in Step A of Example 21 using diisopropyl disulfide instead of diethyl disulfide.

- 25 ¹H-NMR (CDCl₃) δ: 8.17 (d, J= 2.3 Hz, 1H), 7.54 (dd, J= 8.6, 2.3 Hz, 1H), 6.47 (d, J= 8.6 Hz, 1H), 4.59 (br, 2H), 3.14-3.00 (m, 1H), 1.22 (d, J= 6.6 Hz, 6H).

MS (ESI) 169 (M + H)⁺

Step B. 5-(Isopropylsulfonyl)pyridin-2-amine

The title compound was prepared according to the procedure described in Step B of Example 21 using 5-(isopropylthio)pyridin-2-amine (Step A) instead of 5-(ethylthio)pyridin-2-amine.

- 30 ¹H-NMR (CDCl₃) δ: 8.52 (d, J= 2.6 Hz, 1H), 7.81 (dd, J= 8.6, 2.6 Hz, 1H), 6.55 (d, J= 8.6 Hz, 1H), 5.10 (br, 2H), 3.20-3.08 (m, 1H), 1.31 (d, J= 6.6 Hz, 6H).

MS (ESI) 201 (M + H)⁺, 199 (M - H)⁻

Step C. 5-(Isopropylsulfonyl)-3-nitropyridin-2-ol

- 35 The title compound was prepared according to the procedure described in Step C of Example 21 using 5-(isopropylsulfonyl)pyridin-2-amine (Step B) instead of 5-(ethylsulfonyl)pyridin-2-amine.

¹H-NMR (DMSO-d6) δ: 8.54 (d, J= 2.6 Hz, 1H), 8.33 (dd, J= 2.6 Hz, 1H), 3.77-3.17 (m, 1H), 1.21 (d, J= 6.6 Hz, 6H), a peak of OH was not identified.

MS (ESI) 247 ($M + H$)⁺, 245 ($M - H$)⁻

Step D. 2-Chloro-5-(isopropylsulfonyl)-3-nitropyridine

The title compound was prepared according to the procedure described in Step D of Example 21 using 5-(isopropylsulfonyl)-3-nitropyridin-2-ol (Step C) instead of 5-(ethylsulfonyl)-3-nitropyridin-2-ol.

- 5 ¹H-NMR (DMSO-d6) δ: 9.12 (d, $J = 1.7$ Hz, 1H), 8.92 (d, $J = 1.7$ Hz, 1H), 3.70-3.41 (m, 1H), 1.22(d, $J = 6.6$ Hz, 6H).

Step E. 5-(Isopropylsulfonyl)-3-nitro-N-(tetrahydro-2H-pyran-4-ylmethyl)pyridin-2-amine

The title compound was prepared according to the procedure described in Step A of Example 5 from 2-chloro-5-(isopropylsulfonyl)-3-nitropyridine (Step D), 4-(aminomethyl)tetrahydro-2H-pyran-4-ol hydrochloride (Step A of Example 19) and triethylamine.

¹H-NMR (CDCl₃) δ: 8.94 (br, 1H), 8.85 (d, $J = 2.0$ Hz, 1H), 8.74 (d, $J = 2.0$ Hz, 1H), 3.85-3.78 (m, 6H), 3.27-3.17 (m, 1H), 1.84-1.73 (m, 2H), 1.66-1.61 (m, 2H), 1.36 (d, $J = 7.6$ Hz, 6H), a peak of OH was not identified.

MS (ESI) 360 ($M + H$)⁺, 358 ($M - H$)⁻

- 15 Step F. 5-(Isopropylsulfonyl)-N²-(tetrahydro-2H-pyran-4-ylmethyl)pyridin-2,3-diamine

The title compound was prepared according to the procedure described in Step E of Example 1 using 5-(isopropylsulfonyl)-3-nitro-N-(tetrahydro-2H-pyran-4-ylmethyl)pyridin-2-amine (Step E) instead of N-(cyclopropylmethyl)-4-(isopropylsulfonyl)-2-nitroaniline.

- 19 ¹H-NMR (CDCl₃) δ: 8.12 (d, $J = 2.0$ Hz, 1H), 7.21 (d, $J = 2.0$ Hz, 1H), 5.31 (br 1H), 4.77 (br, 1H), 3.83-3.79 (m, 4H), 3.60 (d, $J = 5.9$ Hz, 2H), 3.39 (br, 2H), 3.18-3.08 (m, 1H), 1.74-1.64 (m, 4H), 1.30 (d, $J = 6.6$ Hz, 6H), a peak of OH was not identified.

MS (ESI) 330 ($M + H$)⁺, 328 ($M - H$)⁻

Step G. 4-[{2-(2,2-Dimethylpropyl)-6-(isopropylsulfonyl)-3H-imidazo[4,5-b]pyridin-3-yl}methyl]tetrahydro-2H-pyran-4-ol

- 25 The title compound was prepared according to the procedure described in Step C of Example 17 using 5-(isopropylsulfonyl)-N²-(tetrahydro-2H-pyran-4-ylmethyl)pyridin-2,3-diamine (Step F) instead of 4-(ethylsulfonyl)-N¹-(tetrahydro-2H-pyran-4-ylmethyl)benzene-1,2-diamine.

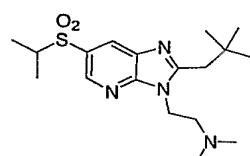
- 29 ¹H-NMR (CDCl₃) δ: 8.77 (d, $J = 2.0$ Hz, 1H), 8.48 (d, $J = 2.0$ Hz, 1H), 4.45 (s, 1H), 4.38 (s, 2H), 3.85-3.71 (m, 4H), 3.32-3.22 (m, 1H), 2.92 (s, 2H), 1.83-1.71 (m, 2H), 1.44-1.40 (m, 2H), 1.36 (d, $J = 6.6$ Hz, 6H), 1.12 (s, 9H), a peak of OH was not identified.

MS (ESI) 410 ($M + H$)⁺, 408 ($M - H$)⁻S

m.p. 179 °C

Example 23

- 35 2-[2-(2,2-Dimethylpropyl)-6-(isopropylsulfonyl)-3H-imidazo[4,5-b]pyridin-3-yl]-N,N-dimethylethana
mine



Step A. N'-[5-(Isopropylsulfonyl)-3-nitropyridin-2-yl]-N,N-dimethylethane-1,2-diamine

The title compound was prepared according to the procedure described in Step A of Example 5 from 2-chloro-5-(isopropylsulfonyl)-3-nitropyridine (Step D of Example 22) and 5 *N,N*-dimethylethylenediamine.

¹H-NMR (CDCl₃) δ: 9.03 (br, 1H), 8.82 (d, J= 2.0 Hz, 1H), 8.76 (d, J= 2.0 Hz, 1H), 3.79-3.72 (m, 2H), 3.26-3.16 (m, 1H), 2.61 (t, J= 5.9 Hz, 2H), 2.32 (s, 6H), 1.35 (d, J= 7.3 Hz, 6H).

MS (ESI) 317 (M + H)⁺, 315 (M - H)⁻

Step B. N²-[2-(Dimethylamino)ethyl]-5-(isopropylsulfonyl)pyridine-2,3-diamine

10 The title compound was prepared according to the procedure described in Step E of Example 1 using *N'*-[5-(isopropylsulfonyl)-3-nitropyridin-2-yl]-*N,N*-dimethylethane-1,2-diamine (Step A) instead of *N*-(cyclopropylmethyl)-4-(isopropylsulfonyl)-2-nitroaniline.

¹H-NMR (CDCl₃) δ: 8.16 (s, 1H), 7.14 (s, 1H), 5.63 (br 1H), 3.65-3.50 (m, 4H), 3.18-3.08 (m, 1H), 2.71-2.67 (m, 2H), 2.36 (s, 6H), 1.30 (d, J= 6.6 Hz, 6H).

15 MS (ESI) 287 (M + H)⁺, 285 (M - H)⁻

Step C. 2-[2-(2,2-Dimethylpropyl)-6-(isopropylsulfonyl)-3*H*-imidazo[4,5-*b*]pyridin-3-yl]-*N,N*-dimethylethanamine

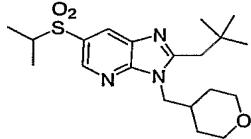
17 The title compound was prepared according to the procedure described in Step C of Example 17 using *N*²-[2-(dimethylamino)ethyl]-5-(isopropylsulfonyl)pyridine-2,3-diamine (Step B) instead of 20 4-(ethylsulfonyl)-*N*¹-(tetrahydro-2*H*-pyran-4-ylmethyl)benzene-1,2-diamine.

¹H-NMR (CDCl₃) δ: 8.80 (d, J= 2.0 Hz, 1H), 8.43 (d, J= 2.0 Hz, 1H), 4.44 (t, J= 7.3 Hz, 2H), 3.31-3.21 (m, 1H), 2.89 (s, 2H), 2.70 (t, J= 7.3 Hz, 2H), 2.32 (s, 6H), 1.35 (d, J= 7.3 Hz, 6H), 1.13 (s, 9H).

MS (ESI) 367 (M + H)⁺

m.p. 119 °C

25

Example 242-(2,2-Dimethylpropyl)-6-(isopropylsulfonyl)-3-(tetrahydro-2*H*-pyran-4-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine

30

Step A. 5-(Isopropylsulfonyl)-3-nitro-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)pyridin-2-amine

The title compound was prepared according to the procedure described in Step A of Example 5 from 2-chloro-5-(isopropylsulfonyl)-3-nitropyridine (Step D of Example 22) and 4-aminomethyltetrahydropyran (Apollo Scientific Ltd.).

35 ¹H-NMR (CDCl₃) δ: 8.83 (d, J= 2.0 Hz, 1H), 8.77 (d, J= 2.0 Hz, 1H), 8.75-8.70 (m, 1H), 4.05-4.00 (m, 2H), 3.67-3.63 (m, 2H), 3.41 (dt, J= 11.9, 2.0 Hz, 2H), 3.27-3.17 (m, 1H), 2.08-1.90 (m, 1H), 1.74-1.70 (m, 2H), 1.51-1.40 (m, 2H), 1.36 (d, J= 7.3 Hz, 6H).

MS (ESI) 344 ($M + H$)⁺, 342 ($M - H$)⁻

Step B. 5-(Isopropylsulfonyl)- N^2 -(tetrahydro-2H-pyran-4-ylmethyl)pyridin-2,3-diamine

The title compound was prepared according to the procedure described in Step E of Example 1 using 5-(isopropylsulfonyl)-3-nitro-N-(tetrahydro-2H-pyran-4-ylmethyl)pyridin-2-amine (Step A) instead of 5 N -(cyclopropylmethyl)-4-(isopropylsulfonyl)-2-nitroaniline.

¹H-NMR (CDCl₃) δ : 8.21 (d, $J = 2.0$ Hz, 1H), 7.20 (d, $J = 2.0$ Hz, 1H), 4.94 (br 1H), 4.03-3.98 (m, 2H), 3.51-3.36 (m, 4H), 3.26 (br, 2H), 3.19-3.09 (m, 1H), 2.03-1.86 (m, 1H), 1.74-1.68 (m, 2H), 1.48-1.35 (m, 2H), 1.31 (d, $J = 7.3$ Hz, 6H).

MS (ESI) 314 ($M + H$)⁺, 312 ($M - H$)⁻

10 Step C. 2-(2,2-Dimethylpropyl)-6-(isopropylsulfonyl)-3-(tetrahydro-2H-pyran-4-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine

The title compound was prepared according to the procedure described in Step C of Example 17 using 5-(isopropylsulfonyl)- N^2 -(tetrahydro-2H-pyran-4-ylmethyl)pyridin-2,3-diamine (Step B) instead of 4-(ethylsulfonyl)- N^1 -(tetrahydro-2H-pyran-4-ylmethyl)benzene-1,2-diamine (Step B of Example 17).

15 ¹H-NMR (CDCl₃) δ : 8.81 (d, $J = 2.0$ Hz, 1H), 8.44 (d, $J = 2.0$ Hz, 1H), 4.23 (d, $J = 7.3$ Hz, 2H), 4.00-3.94 (m, 2H), 3.37-3.25 (m, 3H), 2.87 (s, 2H), 2.32-2.14 (m, 1H), 1.51-1.43 (m, 4H), 1.36 (d, $J = 6.6$ Hz, 6H), 1.13 (s, 9H).

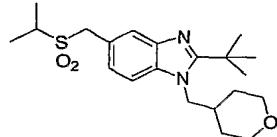
MS (ESI) 394 ($M + H$)⁺

m.p. 201 °C

20

Example 25

2-tert-Butyl-5-[isopropylsulfonyl]methyl]-1-(tetrahydro-2H-pyran-4-ylmethyl)-1*H*-benzimidazole



25 Step A. Methyl 3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]benzoate

The title compound was prepared according to the procedure described in Step A of Example 5 from methyl 4-chloro-3-nitrobenzoate (Lancaster Synthesis Ltd.) and 4-aminomethyltetrahydropyran (Apollo Scientific Ltd.).

30 ¹H-NMR (CDCl₃) δ : 8.90 (d, $J = 2.2$ Hz, 1H), 8.47 (br., 1H), 8.07 (dd $J = 8.8, 2.2$ Hz, 1H), 6.88 (d, $J = 8.8$ Hz, 1H), 4.06-4.01 (m, 2H), 3.91 (s, 3H), 3.48-3.39 (m, 2H), 3.30-3.26 (m, 2H), 2.04-1.74 (m, 3H), 1.52-1.38 (m, 2H).

MS (ESI) 295 ($M + H$)⁺, 293 ($M - H$)⁻.

Step B. Methyl 3-amino-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]benzoate

The title compound was prepared according to the procedure described in step E of Example 1 using methyl 3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]benzoate (step A) instead of N -(cyclopropylmethyl)-4-(isopropylsulfonyl)-2-nitroaniline.

¹H-NMR (CDCl₃) δ : 7.60 (dd, $J = 8.1, 2.2$ Hz, 1H), 7.42 (d, $J = 2.2$ Hz, 1H), 6.59 (d $J = 8.1$ Hz, 1H), 4.09-3.99 (m, 3H), 3.85 (s, 3H), 3.41 (dt, $J = 11.7, 2.2$ Hz, 2H), 3.22 (br., 2H), 3.13-3.08 (m, 2H), 1.98-1.83

(m, 1H), 1.76-1.71 (m, 2H), 1.48-1.34(m, 2H).

MS (ESI) 265 (M + H)⁺, 263 (M - H)⁻.

Step C. Methyl 3-[(2,2-dimethylpropanoyl)amino]-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]benzoate

To a solution of methyl 3-amino-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]benzoate (step B,

5 527 mg, 1.93 mmol) in ethyl acetate (16 mL) was added pivaloyl chloride (256 mg, 2.12 mmol) at room temperature. After stirring for 14 h at room temperature, the mixture was quenched with saturated sodium hydrogencarbonate aqueous solution. The mixture was extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure to afford the title compound (455 mg, 71%) as a white solid.

10 MS (ESI) 349 (M + H)⁺, 348 (M - H)⁻.

Step D. Methyl 2-*tert*-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1*H*-benzimidazole-5-carboxylate

A mixture of methyl 3-[(2,2-dimethylpropanoyl)amino]-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]benzoate (step C, 455 mg,

15 1.31 mmol) and pivalic acid (2.20 g, 21.5 mmol) was stirred at 120°C for 12 h. After cooling to room temperature, the mixture was diluted with dichloromethane. The solution was washed with 1N sodium hydroxide aqueous solution, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 1 : 1 as eluent) to afford the title compound (327 mg, 76%) as a white solid.

¹H-NMR (CDCl₃) δ: 8.48 (s, 1H), 7.97 (d, J= 8.8 Hz, 1H), 7.36 (d, J= 8.8 Hz, 1H), 4.23 (d, J= 7.3 Hz, 2H),

20 4.00-3.95 (m, 2H), 3.93 (s, 3H), 3.36-3.28 (m, 2H), 2.38-2.24 (m, 1H), 1.58 (s, 9H), 1.55-1.46 (m, 4H).

MS (ESI) 331 (M + H)⁺.

.Step E. [2-*tert*-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]methanol

The title compound was prepared according to the procedure described in step D of Example 15 using methyl 2-*tert*-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1*H*-benzimidazole-5-carboxylate (step D) instead of methyl 1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazole-5-carboxylate.

¹H-NMR (CDCl₃) δ: 7.72 (br., 1H), 7.34-7.26 (m, 2H), 4.77 (s, 2H), 4.21 (d, J= 7.3 Hz, 2H), 4.01-3.93 (m, 2H), 3.35-3.27 (m, 2H), 2.37-2.22 (m, 1H), 1.83 (br., 1H), 1.56 (s, 9H), 1.54-1.46 (m, 4H).

MS (ESI) 303 (M + H)⁺.

Step F. 2-*tert*-Butyl-5-(chloromethyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1*H*-benzimidazole

30 The title compound was prepared according to the procedure described in step E of Example 15 using [2-*tert*-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]methanol (step E) instead of [1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazol-5-yl]methanol.

¹H-NMR (CDCl₃) δ: 8.03 (br., 1H), 7.42 (br., 2H), 4.73 (s, 2H), 4.28 (d, J= 7.3 Hz, 2H), 4.07-3.94 (m, 2H), 3.37-3.28 (m, 2H), 2.37-2.22 (m, 1H), 1.64 (s, 9H), 1.60-1.47 (m, 4H).

35 MS (ESI) 321 (M + H)⁺.

Step G. 2-*tert*-Butyl-5-[(isopropylthio)methyl]-1-(tetrahydro-2H-pyran-4-ylmethyl)-1*H*-benzimidazole

The title compound was prepared according to the procedure described in step F of Example 15 using 2-*tert*-butyl-5-(chloromethyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1*H*-benzimidazole (step F) instead of 5-(chloromethyl)-1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazole.

40 ¹H-NMR (CDCl₃) δ: 7.65 (br., 1H), 7.30-7.22 (m, 2H), 4.19 (d, J= 7.3 Hz, 2H), 4.03-3.94 (m, 2H), 3.85 (s,

2H), 3.36-3.28 (m, 2H), 2.81 (heptet, $J= 6.6$ Hz, 1H), 2.38-2.22 (m, 1H), 1.56 (s, 9H), 1.53-1.49 (m, 4H), 1.25 (d, $J= 6.6$ Hz, 6H).

MS (ESI) 361 ($M + H$)⁺.

Step H. 2-tert-Butyl-5-[(isopropylsulfonyl)methyl]-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole

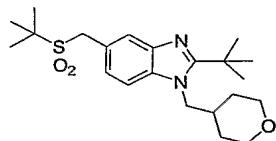
5 The title compound was prepared according to the procedure described in step B of Example 1 using 2-tert-butyl-5-[(isopropylthio)methyl]-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole (step G) instead of 1-chloro-4-(isopropylthio)benzene.

10 ¹H-NMR (CDCl₃) δ: 7.71 (br., 1H), 7.36 (br., 2H), 4.34 (s, 2H), 4.21 (d, $J= 7.3$ Hz, 2H), 4.03-3.95 (m, 2H), 3.40-3.28 (m, 2H), 3.05 (heptet, $J= 6.6$ Hz, 1H), 2.38-2.23 (m, 1H), 1.57 (s, 9H), 1.55-1.48 (m, 4H), 1.37 (d, $J= 6.6$ Hz, 6H).

MS (ESI) 393 ($M + H$)⁺.

Example 26

2-tert-Butyl-5-[(tert-butylsulfonyl)methyl]-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole



15

Step A. 2-tert-Butyl-5-[(tert-butylthio)methyl]-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole

The title compound was prepared according to the procedure described in step F of Example 15 from 2-tert-butyl-5-(chloromethyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole (step F of Example 25) and 2-methyl-2-propanethiol.

¹H-NMR (CDCl₃) δ: 7.69 (br., 1H), 7.27-7.25 (m, 2H), 4.18 (d, $J= 7.3$ Hz, 2H), 4.04-3.93 (m, 2H), 3.88 (s, 2H), 3.35-3.26 (m, 2H), 2.39-2.20 (m, 1H), 1.55 (s, 9H), 1.52-1.45 (m, 4H), 1.36 (s, 9H).

MS (ESI) 375 ($M + H$)⁺.

Step B. 2-tert-Butyl-5-[(tert-butylsulfonyl)methyl]-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole

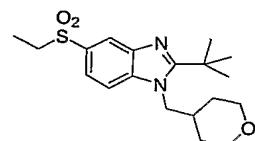
25 The title compound was prepared according to the procedure described in step B of Example 1 using 2-tert-butyl-5-[(tert-butylthio)methyl]-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole (step A) instead of 1-chloro-4-(isopropylthio)benzene.

¹H-NMR (CDCl₃) δ: 7.74 (br., 1H), 7.38-7.32 (m, 2H), 4.32 (s, 2H), 4.20 (d, $J= 7.3$ Hz, 2H), 4.02-3.94 (m, 2H), 3.36-3.28 (m, 2H), 2.37-2.22 (m, 1H), 1.56 (s, 9H), 1.53-1.49 (m, 4H), 1.44 (s, 9H).

30 MS (ESI) 407 ($M + H$)⁺.

Example 27

2-tert-Butyl-5-(ethylsulfonyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole and its hydrochloride salt



35

Step A. 2-*tert*-Butyl-5-(ethylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazole

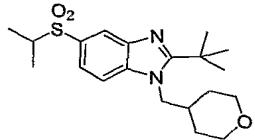
The title compound was prepared according to the procedure described in Step C of Example 17 using pivaloyl chloride instead of *tert*-butylacetyl chloride.

- 5 $^1\text{H-NMR}$ (CDCl_3) δ : 8.32 (d, $J= 1.7$ Hz, 1H), 7.78 (dd, $J= 8.6, 1.7$ Hz, 1H), 7.47 (d, $J= 8.6$ Hz, 1H), 4.28-4.25 (m, 2H), 4.03-3.99 (m, 2H), 3.37-3.28 (m, 2H), 3.15 (q, $J= 7.3$ Hz, 2H), 1.61-1.45 (m, 13H), 1.27 (t, $J= 7.3$ Hz, 3H).

ESI-MS 365 ($\text{M}+\text{H})^+$

Step B. 2-*tert*-Butyl-5-(ethylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazole hydrochloride

- 10 To a solution of 2-*tert*-butyl-5-(ethylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazole (Step A, 113 mg, 0.31 mmol) in ethyl acetate (3 mL) was added 4 N hydrogen chloride in ethyl acetate (1 mL). The mixture was concentrated and the residue was recrystallized from ethyl acetate and methanol to afford the title compound (92.5 mg, 0.23 mmol, 74%) as a white solid.
- 15 $^1\text{H-NMR}$ (CDCl_3) δ : 8.73 (s, 1H), 7.88-7.85 (m, 1H), 7.76-7.73 (m, 1H), 4.49-4.46 (m, 2H), 4.05-4.00 (m, 2H), 3.39-3.31 (m, 2H), 3.12 (q, $J= 7.3$ Hz, 2H), 2.40-2.26 (m, 1H), 1.81 (s, 9H), 1.69-1.49 (m, 4H), 1.24 (t, $J= 7.3$ Hz, 3H).
- ESI-MS 365 ($\text{M}+\text{H})^+$

20 **Example 28**2-*tert*-Butyl-5-(isopropylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazole and its hydrochloride saltStep A. 4-(Isopropylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-nitroaniline

- 25 The title compound was prepared according to the procedure described in Step A of Example 5 using 4-aminomethyltetrahydropyran (Apollo Scientific Ltd.) instead of 1-(2-aminoethyl)pyrrolidine.

$^1\text{H-NMR}$ (CDCl_3) δ : 8.71 (d, $J= 2.3$ Hz, 1H), 8.53 (br, 1H), 7.85 (dd, $J= 8.9, 2.3$ Hz), 6.97 (d, $J= 8.9$ Hz, 1H), 4.08-4.02 (m, 2H), 3.49-3.39 (m, 2H), 3.32-3.27 (m, 2H), 3.25-3.14 (m, 1H), 2.07-1.93 (m, 1H), 1.80-1.75 (m, 2H), 1.54-1.38 (m, 2H), 1.32 (d, $J= 6.6$ Hz, 6H).

30 ESI-MS 343 ($\text{M}+\text{H})^+$, 341 ($\text{M}-\text{H})^-$

Step B. 4-(Isopropylsulfonyl)-*N*¹-(tetrahydro-2*H*-pyran-4-ylmethyl)benzene-1,2-diamine

The title compound was prepared according to the procedure described in Step E of Example 1 using 4-(isopropylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-nitroaniline (Step A) instead of *N*-(cyclopropylmethyl)-4-(isopropylsulfonyl)-2-nitroaniline.

- 35 $^1\text{H-NMR}$ (CDCl_3) δ : 7.36 (dd, $J= 8.2, 2.0$ Hz, 1H), 7.18 (d, $J= 2.0$ Hz), 6.66 (d, $J= 8.2$ Hz, 1H), 4.12-4.00 (m, 3H), 3.51-3.38 (m, 2H), 3.32 (br, 2H), 3.18-3.09 (m, 3H), 2.01-1.81 (m, 1H), 1.77-1.72 (m, 2H), 1.50-1.35 (m, 2H), 1.28 (d, $J= 7.3$ Hz, 6H).

ESI-MS 313 (M+H)⁺, 311 (M-H)

Step C. 2-tert-Butyl-5-(isopropylsulfonyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole

The title compound was prepared according to the procedure described in Step C of Example 17 from 4-(isopropylsulfonyl)-N¹-(tetrahydro-2H-pyran-4-ylmethyl)benzene-1,2-diamine (Step B) and 5 pivaloyl chloride.

¹H-NMR (CDCl₃) δ: 8.30 (d, J= 2.0 Hz, 1H), 7.75 (dd, J= 8.6, 2.0 Hz, 1H), 7.46 (d, J= 8.6 Hz, 1H), 4.28-4.25 (m, 2H), 4.04-3.96 (m, 2H), 3.38-3.17 (m, 3H), 2.39-2.20 (m, 1H), 1.60-1.50 (m, 13H), 1.30 (d, J= 7.3 Hz, 6H).

ESI-MS 379 (M+H)⁺

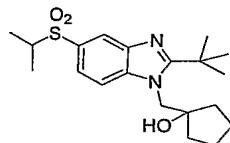
10 Step D. 2-tert-Butyl-5-(isopropylsulfonyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole hydrochloride

The title compound was prepared according to the procedure described in Step B of Example 27 using 2-tert-butyl-5-(isopropylsulfonyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole (Step C) instead of 2-tert-butyl-5-(ethylsulfonyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole.

15 ¹H-NMR (CDCl₃) δ: 8.65 (s, 1H), 7.75 (s, 2H), 4.49 (d, J= 7.3 Hz, 2H), 4.05-4.00 (m, 2H), 3.40-3.31 (m, 2H), 3.25-3.15 (m, 1H), 2.39-2.23 (m, 1H), 1.82 (s, 9H), 1.66-1.49 (m, 4H), 1.23 (d, J= 6.6 Hz, 6H). ESI-MS 379 (M+H)⁺

Example 29

20 1-[{[2-tert-Butyl-5-(isopropylsulfonyl)-1H-benzimidazol-1-yl]methyl}cyclopentanol and its hydrochloride salt



Step A. 1-({[4-(Isopropylsulfonyl)-2-nitrophenyl]amino}methyl)cyclopentanol

The title compound was prepared according to the procedure described in Step A of Example 5 using 1-(aminomethyl)cyclopentanol hydrochloride (*J. Med. Chem.* 1981, 24, 12-16) and triethylamine instead of 1-(2-aminoethyl)pyrrolidine.

¹H-NMR (CDCl₃) δ: 8.79 (br, 1H), 8.70 (d, J= 2.3 Hz, 1H), 7.82 (dd J= 8.9, 2.3 Hz, 1H), 7.02 (d, J= 8.9 Hz, 1H), 3.47 (d, J= 5.3 Hz, 2H), 3.24-3.14 (m, 1H), 1.93-1.61 (m, 9H), 1.32 (t, J= 7.3 Hz, 6H).

MS (ESI) 343 (M + H)⁺, 341 (M - H)⁻

30 Step B. 1-({[2-Amino-4-(isopropylsulfonyl)phenyl]amino}methyl)cyclopentanol

The title compound was prepared according to the procedure described in Step E of Example 1 using 1-({[4-(isopropylsulfonyl)-2-nitrophenyl]amino}methyl)cyclopentanol (Step A) instead of *N*-(cyclopropylmethyl)-4-(isopropylsulfonyl)-2-nitroaniline.

35 ¹H-NMR (CDCl₃) δ: 7.32 (dd, J= 8.8, 2.2 Hz, 1H), 7.16 (d, J= 2.2 Hz, 1H), 6.68 (d, J= 8.8 Hz, 1H), 4.43 (br, 1H), 3.43 (br, 2H), 3.25 (d, J= 5.9 Hz, 2H), 3.17-3.08 (m, 1H), 1.90-1.65 (m, 8H), 1.27 (d, J= 6.6 Hz, 6H), a peak of OH was not identified.

MS (ESI) 313 (M + H)⁺, 311 (M - H)⁻

Step C. 1-[2-*tert*-Butyl-5-(isopropylsulfonyl)-1*H*-benzimidazol-1-yl]methyl)cyclopentanol

The title compound was prepared according to the procedure described in Step C of Example 17 from 1-({[2-amino-4-(isopropylsulfonyl)phenyl]amino}methyl)cyclopentanol (Step B) and pivaloyl chloride.

- 5 $^1\text{H-NMR}$ (CDCl_3) δ : 8.29 (br, 1H), 7.74 (br, 2H), 4.63 (s, 2H), 3.27-3.17 (m, 1H), 1.88-1.70 (m, 8H), 1.58 (s, 9H), 1.30 (d, J = 7.3 Hz, 6H), a peak of OH was not identified.

MS (ESI) 379 ($M + H$) $^+$

Step D. 1-[2-*tert*-Butyl-5-(isopropylsulfonyl)-1*H*-benzimidazol-1-yl]methyl)cyclopentanol hydrochloride

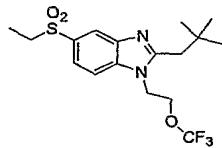
The title compound was prepared according to the procedure described in Step B of Example

- 10 27 using 1-[2-*tert*-butyl-5-(isopropylsulfonyl)-1*H*-benzimidazol-1-yl]methyl)cyclopentanol (Step C) instead of 2-*tert*-butyl-5-(ethylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazole.

$^1\text{H-NMR}$ (CDCl_3) δ : 8.39 (br, 1H), 7.93 (d, J = 8.6 Hz, 1H), 7.84-7.80 (m, 1H), 4.78 (s, 2H), 3.24-3.14 (m, 1H), 2.06-1.44 (m, 17H), 1.21 (d, J = 6.6 Hz, 6H), a peak of OH was not identified.

MS (ESI) 379 ($M + H$) $^+$

15

Example 302-(2,2-Dimethylpropyl)-5-(ethylsulfonyl)-1-[2-(trifluoromethoxy)ethyl]-1*H*-benzimidazoleStep A. 4-(Ethylsulfonyl)-2-nitro-N-[2-(trifluoromethoxy)ethyl]aniline

- 20 The title compound was prepared according to the procedure described in Step A of Example 5 from 1-chloro-4-(ethylsulfonyl)-2-nitrobenzene (Step C of Example 2), 2-(trifluoromethoxy)ethanamine hydrochloride (*J. Org. Chem.* **2001**, 66, 1061-1063.) and triethylamine.

$^1\text{H-NMR}$ (CDCl_3) δ : 8.77 (d, J = 2.0 Hz, 1H), 8.62 (br, 1H), 7.92 (dd J = 9.2, 2.0 Hz, 1H), 7.01 (d, J = 9.2 Hz, 1H), 4.28 (t, J = 5.6 Hz, 2H), 3.79-3.73 (m, 2H), 3.13 (q, J = 7.3 Hz, 2H), 1.31 (t, J = 7.3 Hz, 3H).

- 25 MS (ESI) 343 ($M + H$) $^+$, 341 ($M - H$) $^-$

Step B. 4-(Ethylsulfonyl)-N¹-[2-(trifluoromethoxy)ethyl]benzene-1,2-diamine

The title compound was prepared according to the procedure described in Step E of Example 1 using 4-(ethylsulfonyl)-2-nitro-N-[2-(trifluoromethoxy)ethyl]aniline (Step A) instead of *N*-(cyclopropylmethyl)-4-(isopropylsulfonyl)-2-nitroaniline.

- 30 $^1\text{H-NMR}$ (CDCl_3) δ : 7.39 (dd, J = 8.6, 2.0 Hz, 1H), 7.23 (d, J = 2.0 Hz, 1H), 6.67 (d, J = 8.6 Hz, 1H), 4.24 (t, J = 5.3 Hz, 2H), 3.59-3.47 (m, 3H), 3.44 (br, 2H), 3.07 (q, J = 7.6 Hz, 2H), 1.26 (t, J = 7.6 Hz, 3H).

MS (ESI) 313 ($M + H$) $^+$, 311 ($M - H$) $^-$

Step C. 2-(2,2-Dimethylpropyl)-5-(ethylsulfonyl)-1-[2-(trifluoromethoxy)ethyl]-1*H*-benzimidazole

The title compound was prepared according to the procedure described in Step F of Example 1

- 35 using 4-(ethylsulfonyl)-N¹-[2-(trifluoromethoxy)ethyl]benzene-1,2-diamine (Step B) instead of 2-amino-1-(*N*-cyclopropylmethylamino)-4-(isopropylsulfonyl)benzene.

$^1\text{H-NMR}$ (CDCl_3) δ : 8.33 (s, 1H), 7.85-7.81 (m, 1H), 7.44 (d, J = 8.6 Hz, 1H), 4.55 (t, J = 5.3 Hz, 2H), 4.27 (t,

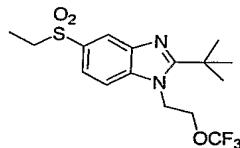
$J = 5.3$ Hz, 2H), 3.17 (q, $J = 7.3$ Hz, 2H), 2.86 (s, 2H), 1.29 (t, $J = 7.3$ Hz, 3H), 1.13 (s, 9H).

MS (ESI) 393 ($M + H$)⁺

m.p. 133 °C

5 Example 31

2-tert-butyl-5-(ethylsulfonyl)-1-[2-(trifluoromethoxy)ethyl]-1*H*-benzimidazole and its hydrochloride salt



Step A. N-(5-(Eethylsulfonyl)-2-{[2-(trifluoromethoxy)ethyl]amino}phenyl)-2,2-dimethylpropanamide

10 To a solution of 4-(ethylsulfonyl)- N^1 -[2-(trifluoromethoxy)ethyl]benzene-1,2-diamine (172 mg, 0.55 mmol, Step B of example 30) in dichloroethane (12 mL) was added pivaloyl chloride (72 mg, 0.6 mmol) at room temperature. After stirring for 24 h, the mixture was quenched with saturated sodium hydrogencarbonate aqueous solution. The organic layer was separated. The aqueous layer was extracted three times with dichloromethane. The combined organic layers were dried over magnesium sulfate and filtered. The filtrate was evaporated under reduced pressure to afford the title compound (187 mg, 86%) as a white solid.

¹H-NMR (CDCl₃) δ: 7.65-7.58 (m, 2H), 7.37 (br., 1H), 6.77 (d, $J = 8.8$ Hz, 1H), 4.21 (t $J = 5.1$ Hz, 2H), 3.51 (t, $J = 5.1$ Hz, 2H), 3.08 (q, $J = 7.3$ Hz, 2H), 1.37 (br., 1H), 1.35 (s, 9H), 1.27 (t, $J = 7.3$ Hz, 3H).

MS (ESI) 397 ($M + H$)⁺, 395 ($M - H$)⁻.

20 Step B. 2-tert-Butyl-5-(ethylsulfonyl)-1-[2-(trifluoromethoxy)ethyl]-1*H*-benzimidazole

N-(5-(Eethylsulfonyl)-2-{[2-(trifluoromethoxy)ethyl]amino}phenyl)-2,2-dimethylpropanamide (187 mg, 0.47 mmol, step A) was dissolved in ethanol and 2N sodium hydroxide solution. The mixture was microwaved for 30 min at 140 °C. The reaction mixture was quenched with water and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate and filtered. The filtrate was evaporated under reduced pressure. The residue was purified by PTLC (hexane : acetone = 3 : 1 as eluent) to afford the title compound (60 mg, 34%) as a yellow oil.

¹H-NMR (CDCl₃) δ: 8.33 (d, $J = 1.5$ Hz, 1H), 7.82 (dd, $J = 8.8, 1.5$ Hz, 1H), 7.48 (d, $J = 8.8$ Hz, 1H), 4.73 (t $J = 6.6$ Hz, 2H), 4.35 (t, $J = 6.6$ Hz, 2H), 3.14 (q, $J = 7.3$ Hz, 2H), 1.59 (s, 9H), 1.26 (t, $J = 7.3$ Hz, 3H).

MS (ESI) 379 ($M + H$)⁺.

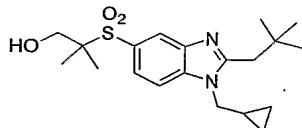
30 Step C. 2-tert-Butyl-5-(ethylsulfonyl)-1-[2-(trifluoromethoxy)ethyl]-1*H*-benzimidazole hydrochloride

The title compound was prepared according to the procedure described in Step B of Example 27 using 2-tert-butyl-5-(ethylsulfonyl)-1-[2-(trifluoromethoxy)ethyl]-1*H*-benzimidazole (Step B) instead of 2-tert-butyl-5-(ethylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazole.

¹H-NMR (DMSO_d₆) δ: 8.25 (d, $J = 1.5$ Hz, 1H), 8.07 (d, $J = 8.8$ Hz, 1H), 7.91 (dd, $J = 8.8, 1.5$ Hz, 1H), 5.01

35 (t, $J = 5.1$ Hz, 2H), 4.55 (t, $J = 5.1$ Hz, 2H), 3.36 (q, $J = 7.3$ Hz, 2H), 1.58 (s, 9H), 1.09 (t, $J = 7.3$ Hz, 3H).

MS (ESI) 379 ($M + H$)⁺.

Example 32**2-[{1-(Cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1H-benzimidazol-5-yl}sulfonyl]-2-methylpropan-1-ol****5 Step A. 4-Bromo-N-(cyclopropylmethyl)-2-nitroaniline**

A mixture of 1,4-dibromo-2-nitrobenzene (750 mg, 2.7 mmol) and cyclopropanemethylamine (579 μ L, 6.7 mmol) was stirred at 80 °C for 18 h. The mixture was purified by column chromatography on silica gel (ethyl acetate as eluent) to afford the title compound (723 mg, 100%) as an orange solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 8.32 (d, $J=2.4$ Hz, 1H), 8.11 (br, 1H), 7.49-7.46 (m, 1H), 6.72 (d, $J=9.2$ Hz, 1H),

10 3.16-3.11 (m, 2H), 1.20-1.14 (m, 1H), 0.69-0.62 (m, 2H), 0.35-0.29 (m, 2H).

MS (ESI) 271 ($M + H$) $^+$.

Step B. 4-Bromo-N¹-(cyclopropylmethyl)benzene-1,2-diamine

A mixture of 4-bromo-N-(cyclopropylmethyl)-2-nitroaniline (Step A, 1.7 g, 6.2 mmol), iron (1.7 g, 31.2 mmol) and ammonium chloride (33 mg, 0.62 mmol) in ethanol (18 mL) and water (6 mL) was stirred under reflux for 4 h. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated. The residue was dissolved in ethyl acetate (40 mL) and the mixture was washed with water containing aqueous ammonia. The organic layer was separated, dried over sodium sulfate and concentrated to afford the title compound (1.48 g, 98%) as a brown oil.

$^1\text{H-NMR}$ (CDCl_3) δ : 6.88 (dd, $J=8.4, 2.2$ Hz, 1H), 6.83 (d, $J=2.2$ Hz, 1H), 6.47 (d, $J=8.4$ Hz, 1H), 3.41

20 (br., 3H), 2.90 (d, $J=6.8$ Hz, 1H), 1.19-1.06 (m, 1H), 0.60-0.54 (m, 2H), 0.27-0.22 (m, 2H).

MS (ESI) 241 ($M + H$) $^+$.

Step C. 5-Bromo-1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1H-benzimidazole and**N-{5-bromo-2-[(cyclopropylmethyl)amino]phenyl}-3,3-dimethylbutanamide**

To a solution of 4-bromo-N¹-(cyclopropylmethyl)benzene-1,2-diamine (Step B, 1.48 g, 6.15 mmol) in ethyl acetate (30 mL) was added *tert*-butylacetyl chloride (940 μ L, 6.77 mmol) at room temperature. After stirring for 1 h, *p*-toluenesulfonic acid monohydrate (1.29 g, 6.77 mmol) was added and the mixture was stirred under reflux for 9 h. Water (20 mL) and aqueous ammonia (10 mL) were added and the mixture was extracted with ethyl acetate (30 mL x 2) and washed with brine (10 mL). The organic extracts were dried over sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 9 : 1 as eluent) to give 5-bromo-1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1H-benzimidazole (965 mg, 49%) as a brown oil and N-{5-Bromo-2-[(cyclopropylmethyl)amino]phenyl}-3,3-dimethylbutanamide (761 mg, 36%) as a white solid.

5-Bromo-1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1H-benzimidazole:

35 $^1\text{H-NMR}$ (CDCl_3) δ : 7.88 (d, $J=1.8$ Hz, 1H), 7.33 (dd, $J=8.5, 1.8$ Hz, 1H), 7.22 (d, $J=8.5$ Hz, 1H), 4.05 (d, $J=7.2$ Hz, 2H), 2.80 (s, 2H), 1.19-1.10 (m, 1H), 1.07 (s, 9H), 0.63-0.57 (m, 2H), 0.38-0.33 (m, 2H).

MS (ESI) 321 ($M + H$) $^+$.

N-{5-Bromo-2-[(cyclopropylmethyl)amino]phenyl}-3,3-dimethylbutanamide:

¹H-NMR (CDCl₃) δ: 7.42 (d, J= 2.0 Hz, 1H), 7.21(dd, J= 8.6, 2.0 Hz, 1H), 6.97 (br., 1H), 6.59 (d, J= 8.6 Hz, 1H), 3.95 (br., 1H), 2.89 (d, J= 7.1 Hz, 2H), 2.28 (s, 2H), 1.14-0.98 (m, 10H), 0.61-0.52 (m, 2H), 0.27-0.21 (m, 2H).

MS (ESI) 339 (M + H)⁺, 337 (M - H)⁻.

5 **Step D. 5-Bromo-1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazole**

A mixture of *N*-(5-bromo-2-[(cyclopropylmethyl)amino]phenyl)-3,3-dimethylbutanamide (Step C, 761 mg, 2.24 mmol) and *p*-toluenesulfonic acid monohydrate (426 mg, 2.24 mmol) in toluene (40 mL) was stirred under reflux for 23 h with Dean-Stark apparatus. Water (10 mL) and aqueous ammonia (5 mL) were added and the mixture was extracted with ethyl acetate (20 mL × 2). The organic extracts were dried over sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 9 : 1 as eluent) to give the title compound (651 mg, 90%) as a brown oil.

10 ¹H-NMR (CDCl₃) δ: 7.88 (d, J= 1.8 Hz, 1H), 7.33 (dd, J= 8.5, 1.8 Hz, 1H), 7.22 (d, J= 8.5 Hz, 1H), 4.05 (d, J= 7.2 Hz, 2H), 2.80 (s, 2H), 1.19-1.10 (m, 1H), 1.07 (s, 9H), 0.63-0.57 (m, 2H), 0.38-0.33 (m, 2H).

15 MS (ESI) 321 (M + H)⁺.

Step E. Methyl {[1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazol-5-yl]thio}acetate

To a solution of 5-bromo-1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazole (Step D, 1.40 g, 4.36 mmol) in 1,4-dioxane (9 mL) were added *N,N*-diisopropylethylamine (1.52 mL, 8.72 mmol), methyl mercaptoacetate (0.39 mL, 4.36 mmol), tris(dibenzylideneacetone)dipalladium(0) (200 mg, 0.218 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (252 mg, 0.436 mmol). The mixture was heated to reflux for 21 h under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to give a dark brown syrup. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 5 : 1 as eluent) to afford the title compound (1.95 g, quant.) as an orange syrup.

25 ¹H-NMR (CDCl₃) δ: 7.88 (d, J= 1.5 Hz, 1H), 7.37 (dd, J= 8.1, 1.5 Hz, 1H), 7.30 (d, J= 8.1 Hz, 1H), 4.05 (d, J= 6.6 Hz, 2H), 3.71 (s, 3H), 3.64 (s, 2H), 2.81 (s, 2H), 1.22-1.13 (m, 1H), 1.08 (s, 9H), 0.63-0.57 (m, 2H), 0.39-0.34 (m, 2H).

Step F. Methyl {[1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazol-5-yl]sulfonyl}acetate

The title compound was prepared according to the procedure described in Step B of Example 1 using 30 methyl {[1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazol-5-yl]thio}acetate (Step E) instead of 1-chloro-4-(isopropylthio)benzene.

¹H-NMR (CDCl₃) δ: 8.35 (br s, 1H), 7.83 (dd, J= 8.8, 1.5 Hz, 1H), 7.50 (d, J= 8.8 Hz, 1H), 4.17 (s, 2H), 4.12 (d, J= 6.6 Hz, 2H), 3.73 (s, 3H), 2.86 (s, 2H), 1.15-1.06 (m, 10H), 0.70-0.60 (m, 2H), 0.44-0.35 (m, 2H).

35 MS (ESI) 379 (M+H)⁺.

Step G. Methyl

2-{[1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazol-5-yl]sulfonyl}-2-methylpropanoate

To a solution of methyl {[1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazol-5-yl]sulfonyl}acetate (Step F, 990 mg, 2.61 mmol) in *N,N*-dimethylformamide (10 mL) was added sodium hydride (230 mg, 5.75 mmol) and

methyl iodide (350 μ L, 5.75 mmol) at 0 °C. After stirring for 3 h at room temperature, the mixture was quenched with water and extracted three times with ethyl acetate. The combined organic layers were dried over sodium sulfate and filtered. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 3 : 1 as eluent) to afford the title compound

5 (852 mg, 80%) as a yellow viscous oil.

1 H-NMR (CDCl₃) δ : 8.26 (br s, 1H), 7.71 (dd, J = 8.1, 2.2 Hz, 1H), 7.46 (d, J = 8.1 Hz, 1H), 4.12 (d, J = 6.6 Hz, 2H), 3.71 (s, 3H), 2.85 (s, 2H), 1.65 (s, 6H), 1.20-1.03 (m, 10H), 0.71-0.57 (m, 2H), 0.46-0.32 (m, 2H). MS (ESI) 407 (M+H)⁺.

Step H.

10 2-[1-(Cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazol-5-yl]sulfonyl]-2-methylpropan-1-ol

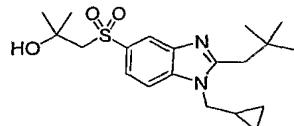
To a suspension of lithium aluminum hydride (37 mg, 0.98 mmol) in tetrahydrofuran (4 mL) was added a solution of 2-[1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazol-5-yl]sulfonyl]-2-methylpropanoate (Step G, 400 mg, 0.98 mmol) in tetrahydrofuran (4 mL) at 0 °C. After stirring for 3 h at 0°C, the mixture was quenched with potassium fluoride (170 mg, 2.96 mmol) and sodium sulfate decahydrate (1.26 g, 3.92 mmol) at 0 °C, filtered through a pad of celite and concentrated. The resulting residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 1 : 1 as eluent) to afford the title compound (345 mg, 93%) as a white amorphous solid.

15 1 H-NMR (CDCl₃) δ : 8.29 (d, J = 2.2 Hz, 1H), 7.75 (dd, J = 8.8, 1.5 Hz, 1H), 7.49 (d J = 8.8 Hz, 1H), 4.13 (d, J = 6.6 Hz, 2H), 3.76 (d, J = 6.6 Hz, 2H), 3.09 (t, J = 6.6 Hz, 1H), 2.86 (s, 2H), 1.34 (s, 6H), 1.17-1.07 (m, 10H), 0.71-0.60 (m, 2H), 0.45-0.35 (m, 2H).

20 MS (ESI) 379 (M + H)⁺.

Example 33

25 1-[1-(Cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazol-5-yl]sulfonyl]-2-methylpropan-2-ol



To a solution of 1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-(methylsulfonyl)-1*H*-benzimidazole (Example 4, 67 mg, 0.21 mmol) in tetrahydrofuran was added lithium bis(trimethylsilyl)amide (1.06 M in hexane, 217 μ L, 0.23 mmol) at -40°C under nitrogen atmosphere. After stirring for 5 min, excess acetone was added at -40°C and the mixture was allowed to warm to room temperature. After stirring for 18 h, the mixture was quenched with saturated ammonium chloride aqueous solution and extracted three times with ethyl acetate. The combined organic layers were dried over sodium sulfate and filtered. The filtrate was concentrated and the residue was purified by PTLC (hexane : ethyl acetate = 1 : 1, three times) to afford the title compound (6.4 mg, 8%) as a white amorphous solid.

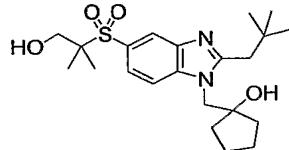
30 1 H-NMR (CDCl₃) δ : 8.33 (d, J = 1.5 Hz, 1H), 7.80 (dd, J = 8.8, 1.5 Hz, 1H), 7.50 (d J = 8.8 Hz, 1H), 4.13 (d, J = 6.6 Hz, 2H), 3.89 (s, 1H), 3.36 (s, 2H), 2.86 (s, 2H), 1.46 (s, 6H), 1.28-1.19 (m, 1H), 1.10 (s, 9H),

0.68-0.59 (m, 2H), 0.43-0.35 (m, 2H).

MS (ESI) 379 (M + H)⁺.

Example 34

- 5 **1-{[2-(2,2-Dimethylpropyl)-5-[(2-hydroxy-1,1-dimethylethyl)sulfonyl]-1*H*-benzimidazol-1-yl]methyl}cyclopentanol**



Step A. 1-{[(4-Bromo-2-nitrophenyl)amino]methyl}cyclopentanol

The mixture of 2,5-dibromonitrobenzene (Tokyo Kasei Kogyo Co., Ltd., 5.4 g, 19.2 mmol),
10 1-(aminomethyl)cyclopentanol hydrochloride (*J. Med. Chem.* 1981, 24, 12-16, 4.3 g, 28.4 mmol) and
N,N-diisopropylethylamine (8.4 mL, 48.1 mmol) in 1-methyl-2-pyrrolidinone (32 mL) was microwaved for
30 min at 200 °C. The reaction was quenched with water and extracted three times with ethyl acetate.
The combined organic layers were dried over sodium sulfate and filtered. The filtrate was concentrated
and the residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 5 : 1 as
15 eluent) to afford the title compound (2.6 g, 43%) as an orange amorphous solid.

¹H-NMR (CDCl₃) δ: 8.36 (br s, 1H), 8.32 (d, J= 2.2 Hz, 1H), 7.49 (dd, J= 8.8, 2.2 Hz, 1H), 6.83 (d, J= 9.5
Hz, 1H), 3.40 (d, J= 5.1 Hz, 2H), 1.96-1.67 (m, 8H), a peak of OH was not identified.
MS (ESI) 315 (M + H)⁺, 313 (M - H)⁻.

Step B. 1-{[(2-Amino-4-bromophenyl)amino]methyl}cyclopentanol

20 The title compound was prepared according to the procedure described in Step B of Example
32 using 1-{[(4-bromo-2-nitrophenyl)amino]methyl}cyclopentanol (Step A) instead of
4-bromo-N-(cyclopropylmethyl)-2-nitroaniline.
¹H-NMR (CDCl₃) δ: 6.89 (dd, J= 8.8, 2.2 Hz, 1H), 6.84 (d, J= 2.2 Hz, 1H), 6.54 (d, J= 8.1, 1H), 3.50 (br s,
2H), 3.14 (s, 2H), 1.95-1.62 (m, 8H), peaks of OH and NH were not identified.
25 MS (ESI) 285 (M + H)⁺.

Step C. 1-{[5-Bromo-2-(2,2-dimethylpropyl)-1*H*-benzimidazol-1-yl]methyl}cyclopentanol

The title compound was prepared according to the procedure described in Step F of Example 1
using 1-{[(2-amino-4-bromophenyl)amino]methyl}cyclopentanol (Step B) instead of
2-amino-1-(*N*-cyclopropylmethylamino)-4-(isopropylsulfonyl)benzene.
30 ¹H-NMR (CDCl₃) δ: 7.86 (br s, 1H), 7.31 (m, 2H), 4.31 (s, 2H), 2.90 (s, 2H), 1.92-1.52 (m, 8H), 1.32 (s,
1H), 1.05 (s, 9H).
MS (ESI) 365 (M + H)⁺.

Step D. Methyl

(2-(2,2-dimethylpropyl)-1-[(1-hydroxycyclopentyl)methyl]-1*H*-benzimidazol-5-yl)thio)acetate

35 The title compound was prepared according to the procedure described in Step E of Example
32 using 1-{[5-bromo-2-(2,2-dimethylpropyl)-1*H*-benzimidazol-1-yl]methyl}cyclopentanol (Step C) instead
of 5-bromo-1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazole.

¹H-NMR (CDCl₃) δ: 7.85 (br s, 1H), 7.35 (m, 2H), 4.31 (s, 2H), 3.71 (s, 3H), 3.65 (s, 2H), 2.91 (s, 2H), 1.92-1.60 (m, 8H), 1.06 (s, 9H), a peak of OH was not identified.

MS (ESI) 391 (M + H)⁺.

Step E. Methyl

5 ({2-(2,2-dimethylpropyl)-1-[(1-hydroxycyclopentyl)methyl]-1H-benzimidazol-5-yl}sulfonyl)acetate

The title compound was prepared according to the procedure described in Step B of Example 1 using methyl ({2-(2,2-dimethylpropyl)-1-[(1-hydroxycyclopentyl)methyl]-1H-benzimidazol-5-yl}thio)acetate (Step D) instead of 1-chloro-4-(isopropylthio)benzene.

10 ¹H-NMR (CDCl₃) δ: 8.33 (d, J= 1.5Hz, 1H), 7.79 (dd, J= 8.8, 1.5Hz, 1H), 7.59 (d, J= 8.8 Hz, 1H), 4.37 (s,

10 ¹⁰ 2H), 4.16 (s, 2H), 3.73 (s, 3H), 2.96 (s, 2H), 1.91-1.60 (m, 8H), 1.08 (s, 9H), a peak of OH was not identified.

MS (ESI) 423 (M + H)⁺, 421(M - H)⁻.

Step F. Methyl

2-{(2-(2,2-dimethylpropyl)-1-[(1-hydroxycyclopentyl)methyl]-1H-benzimidazol-5-yl}sulfonyl)-2-methylpropanoate

15 noate

The title compound was prepared according to the procedure described in Step G of Example 32 using methyl ({2-(2,2-dimethylpropyl)-1-[(1-hydroxycyclopentyl)methyl]-1H-benzimidazol-5-yl}sulfonyl)acetate (Step E) instead of methyl {[1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1H-benzimidazol-5-yl]sulfonyl}acetate.

20 ¹H-NMR (CDCl₃) δ: 8.25 (d, J= 1.5Hz, 1H), 7.68 (dd, J= 8.8, 1.5Hz, 1H), 7.54 (d, J= 8.8 Hz, 1H), 4.37 (s, 2H), 3.71 (s, 3H), 2.95 (s, 2H), 1.94-1.60 (m, 8H), 1.65 (s, 6H), 1.38 (s, 1H), 1.08 (s, 9H)

MS (ESI) 451 (M + H)⁺.

Step G.

1-{(2-(2,2-Dimethylpropyl)-5-[(2-hydroxy-1,1-dimethylethyl)sulfonyl]-1H-benzimidazol-1-yl)methyl)cyclopentanol

25 ntanol

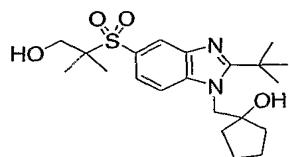
The title compound was prepared according to the procedure described in Step H of Example 32 using methyl 2-{(2-(2,2-dimethylpropyl)-1-[(1-hydroxycyclopentyl)methyl]-1H-benzimidazol-5-yl}sulfonyl)-2-methylpropanoate (Step F) instead of 2-{[1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1H-benzimidazol-5-yl]sulfonyl}-2-methylpropanoate.

30 ¹H-NMR (CDCl₃) δ: 8.29 (d, J= 1.5Hz, 1H), 7.73 (dd, J= 8.8, 1.5Hz, 1H), 7.58 (d, J= 8.1 Hz, 1H), 4.38 (s, 2H), 3.75 (d, J= 6.6Hz, 2H), 3.06 (t, J= 6.6Hz, 2H), 2.96 (s, 2H), 1.89-1.60 (m, 8H), 1.34 (s, 6H), 1.33 (s, 1H), 1.09 (s, 9H).

MS (ESI) 423 (M + H)⁺.

35 Example 35

1-{(2-tert-Butyl-5-[(2-hydroxy-1,1-dimethylethyl)sulfonyl]-1H-benzimidazol-1-yl)methyl)cyclopentanol



Step A. N-(5-Bromo-2-{[(1-hydroxycyclopentyl)methyl]amino}phenyl)-2,2-dimethylpropanamide

To a solution of 1-{[(2-amino-4-bromophenyl)amino]methyl}cyclopentanol (Step B of Example 34, 5 1.3 g, 4.15 mmol) in ethyl acetate (100 mL) was added pivaloyl chloride (511 mg, 4.15 mmol) at room temperature. After stirring for 2 h at room temperature, the mixture was quenched with saturated sodium hydrogencarbonate aqueous solution. The mixture was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 5 : 1 as eluent) to afford the title compound (1.3 g, 10 75%) as a beige amorphous solid.

¹H-NMR (CDCl₃) δ: 7.43 (d, J= 2.2Hz, 1H), 7.31 (br s, 1H), 7.22 (dd, J= 8.1, 2.2Hz, 1H), 6.69 (d, J= 8.8Hz, 1H), 4.07 (br s, 1H), 3.17 (d, J= 3.7Hz, 2H), 2.12 (s, 1H), 1.93-1.61 (m, 8H), 1.34 (s, 9H).
MS (ESI) 371 (M + H)⁺, 369 (M - H).

Step B. 1-[(5-Bromo-2-*tert*-butyl-1*H*-benzimidazol-1-yl)methyl]cyclopentanol

15 To a solution of N-(5-bromo-2-{[(1-hydroxycyclopentyl)methyl]amino}phenyl)-2,2-dimethylpropanamide (Step A, 1.3 g, 3.41 mmol) in toluene (100 mL) was added *p*-toluenesulfonic acid monohydrate (130 mg, 0.68 mmol) at room temperature and the mixture was stirred at 140 °C for 23h. After cooling to room temperature, *p*-toluenesulfonic acid monohydrate (130 mg, 0.68 mmol) was added, and the mixture was heated at 140 20 °C. After stirring for 26 h at 140 °C, the mixture was quenched with saturated sodium hydrogencarbonate aqueous solution. The mixture was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate : dichloromethane = 5.5 : 1 : 0.5 as eluent) to afford the title compound (453 mg, 38%) as a beige amorphous solid.

25 ¹H-NMR (CDCl₃) δ: 7.88 (d, J= 2.2Hz, 1H), 7.43 (d, J= 8.8Hz, 1H), 7.30 (dd, J= 8.8, 2.2Hz, 1H), 4.55 (s, 2H), 1.88-1.69 (m, 8H), 1.57 (s, 9H), 1.22 (s, 1H).
MS (ESI) 353 (M + H)⁺.

Step C. Methyl ({2-*tert*-butyl-1-[(1-hydroxycyclopentyl)methyl]-1*H*-benzimidazol-5-yl}thio)acetate

The title compound was prepared according to the procedure described in Step E of Example 32 using 30 1-[(5-bromo-2-*tert*-butyl-1*H*-benzimidazol-1-yl)methyl]cyclopentanol (Step B) instead of 5-bromo-1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazole.

¹H-NMR (CDCl₃) δ: 7.86 (d, J= 1.5 Hz, 1H), 7.49 (d, J= 8.8 Hz, 1H), 7.33 (dd, J= 8.8, 1.5 Hz, 1H), 4.55 (s, 2H), 3.71 (s, 3H), 3.63 (s, 2H), 1.89-1.70 (m, 8H), 1.57 (s, 9H), 1.24 (s, 1H).
MS (ESI) 377 (M + H)⁺.

35 **Step D. Methyl ({2-*tert*-butyl-1-[(1-hydroxycyclopentyl)methyl]-1*H*-benzimidazol-5-yl}sulfonyl)acetate**

The title compound was prepared according to the procedure described in Step B of Example 1 using methyl ({2-*tert*-butyl-1-[(1-hydroxycyclopentyl)methyl]-1*H*-benzimidazol-5-yl}thio)acetate (Step C) instead

of 1-chloro-4-(isopropylthio)benzene.

¹H-NMR (CDCl₃) δ: 8.35 (s, 1H), 7.78 (br s, 2H), 4.63 (s, 2H), 4.15 (s, 2H), 3.72 (s, 3H), 1.90-1.70 (m, 8H), 1.60 (s, 9H), a peak of OH was not identified.

MS (ESI) 409 (M + H)⁺, 369 (M - H)⁻.

5 Step E. Methyl

2-((2-tert-butyl-1-[(1-hydroxycyclopentyl)methyl]-1*H*-benzimidazol-5-yl)sulfonyl)-2-methylpropanoate

The title compound was prepared according to the procedure described in Step G of Example 32 using methyl ((2-tert-butyl-1-[(1-hydroxycyclopentyl)methyl]-1*H*-benzimidazol-5-yl)sulfonyl)acetate (Step D) instead of methyl {[1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazol-5-yl]sulfonyl}acetate.

10 ¹H-NMR (CDCl₃) δ: 8.26 (d, J = 1.5Hz, 1H), 7.73 (d, J = 8.8Hz, 1H), 7.65 (dd, J = 8.8, 1.5Hz, 1H), 4.62 (s, 2H), 3.72 (s, 3H), 1.88-1.70 (m, 8H), 1.63 (s, 6H), 1.60 (s, 9H), 1.35 (s, 1H).

MS (ESI) 437 (M + H)⁺.

Step F.

1-((2-tert-Butyl-5-[(2-hydroxy-1,1-dimethylethyl)sulfonyl]-1*H*-benzimidazol-1-yl)methyl)cyclopentanol

15 The title compound was prepared according to the procedure described in Step H of Example 32 using methyl 2-((2-tert-butyl-1-[(1-hydroxycyclopentyl)methyl]-1*H*-benzimidazol-5-yl)sulfonyl)-2-methyl propanoate (Step E) instead of methyl 2-[(1-cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazol-5-yl]sulfonyl)-2-methylpropanoate.

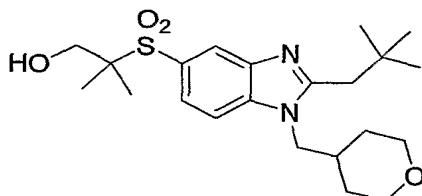
¹H-NMR (CDCl₃) δ: 8.29 (d, J = 1.5Hz, 1H), 7.78 (d, J = 8.8Hz, 1H), 7.71 (dd, J = 8.8, 1.5Hz, 1H), 4.64 (s,

20 2H), 3.74 (d, J = 6.6Hz, 2H), 3.06 (t, J = 6.6Hz, 2H), 1.87-1.70 (m, 8H), 1.60 (s, 9H), 1.34 (s, 1H), 1.33 (s, 6H).

MS (ESI) 409 (M + H)⁺.

Example 36

25 2-[(2-(2,2-Dimethylpropyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]sulfonyl]-2-methylpropan-1-ol and its hydrochloride salt



Step A. 4-Bromo-2-nitro-N-(tetrahydro-2*H*-pyran-4-ylmethyl)aniline

The title compound was prepared according to the procedure described in Step A of Example 5 from 4-bromo-1-fluoro-2-nitrobenzene (Wako Pure Chemical Industries, Ltd.) and 4-aminomethyltetrahydropyran (Apollo Scientific Ltd.).

¹H-NMR (CDCl₃) δ: 8.33 (d, J = 2.6 Hz, 1H), 8.14 (br, 1H), 7.51 (dd, J = 9.2, 2.6 Hz, 1H), 6.77 (d, J = 9.2 Hz, 1H), 4.03 (dd, J = 10.9, 4.3 Hz, 2H), 3.42 (dt, J = 11.7, 2.3 Hz, 2H), 3.21 (dd, J = 6.9, 5.6 Hz, 2H), 2.02-1.87 (m, 1H), 1.78-1.72 (m, 2H), 1.51-1.35 (m, 2H).

35 MS (ESI) 315 (M + H)⁺.

Step B. 4-Bromo-N¹-(tetrahydro-2*H*-pyran-4-ylmethyl)benzene-1,2-diamine

The title compound was prepared according to the procedure described in Step B of Example 32 using 4-bromo-2-nitro-N-(tetrahydro-2H-pyran-4-ylmethyl)aniline (Step A) instead of 4-bromo-N-(cyclopropylmethyl)-2-nitroaniline.

¹H-NMR (CDCl₃) δ: 6.92 (dd, J= 8.6, 2.3 Hz, 1H), 6.85 (d, J= 2.3 Hz, 1H), 6.45 (d, J= 8.6 Hz, 1H), 5.04-3.98 (m, 2H), 3.46-3.34 (m, 5H), 2.99 (d, J= 6.6 Hz, 2H), 1.96-1.79 (m, 1H), 1.76-1.71 (m, 2H), 1.48-1.33 (m, 2H).

MS (ESI) 285 (M + H)⁺.

Step C. 5-Bromo-2-(2,2-dimethylpropyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole

The title compound was prepared according to the procedure described in Step F of Example 10 using 4-bromo-N¹-(tetrahydro-2H-pyran-4-ylmethyl)benzene-1,2-diamine (Step B) instead of 2-amino-1-(N-cyclopropylmethylamino)-4-(isopropylsulfonyl)benzene.

¹H-NMR (CDCl₃) δ: 7.88 (d, J= 1.7 Hz, 1H), 7.34 (dd, J= 8.6, 1.7 Hz, 1H), 7.17 (d, J= 8.6 Hz, 1H), 4.03 (d, J= 7.3 Hz, 2H), 3.99-3.93 (m, 2H), 3.33-3.24 (m, 2H), 2.79 (s, 2H), 2.12-1.98 (m, 1H), 1.46-1.38 (m, 4H), 1.07 (s, 9H).

15 MS (ESI) 365 (M + H)⁺.

Step D. Methyl

{[2-(2,2-dimethylpropyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]thio}acetate

A mixture of 5-bromo-2-(2,2-dimethylpropyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole (Step C, 300 mg, 0.82 mmol), N,N-diisopropylethylamine (286 μL, 1.64 mmol), methyl mercaptoacetate (73 μL, 0.82 mmol), tris(dibenzylideneacetone)dipalladium(0) (37.5 mg, 0.041 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (47.4 mg, 0.082 mmol) in 1,4-dioxane was microwaved at 120 °C for 30 min. The reaction mixture was cooled to room temperature and filtered through a pad of celite. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 3 : 2 then 1 : 1 as eluent) to afford the title compound (318 mg, 99%) as a yellow viscous oil.

¹H-NMR (CDCl₃) δ: 7.87 (d, J= 2.0 Hz, 1H), 7.38 (dd, J= 8.6, 2.0 Hz, 1H), 7.24 (d, J= 8.6 Hz, 1H), 4.03 (d, J= 7.3 Hz, 2H), 3.98-3.93 (m, 2H), 3.72 (s, 3H), 3.65 (s, 2H), 3.34-3.25 (m, 2H), 2.79 (s, 2H), 2.16-2.00 (m, 1H), 1.65-1.63 (m, 2H), 1.47-1.39 (m, 2H), 1.08 (s, 9H).

MS (ESI) 391 (M + H)⁺.

30 Step E. Methyl

{[2-(2,2-dimethylpropyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]sulfonyl}acetate

The title compound was prepared according to the procedure described in Step B of Example 1 using methyl {[2-(2,2-dimethylpropyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]thio}acetate (Step D) instead of 1-chloro-4-(isopropylthio)benzene.

35 ¹H-NMR (CDCl₃) δ: 8.35 (d, J= 1.7 Hz, 1H), 7.83 (dd, J= 8.6, 1.7 Hz, 1H), 7.45 (d, J= 8.6 Hz, 1H), 4.17 (s, 2H), 4.14-4.09 (m, 2H), 4.01-3.95 (m, 2H), 3.74 (s, 3H), 3.35-3.26 (m, 2H), 2.84 (s, 2H), 2.15-2.01 (m, 1H), 1.49-1.41 (m, 4H), 1.10 (s, 9H).

MS (ESI) 423 (M + H)⁺.

Step F. Methyl

40 {[2-(2,2-dimethylpropyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]sulfonyl}-2-methylpropa

noate

The title compound was prepared according to the procedure described in Step G of Example 32 using methyl {[2-(2,2-dimethylpropyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]sulfonyl}acetate (Step E) instead of methyl

- 5 {[1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazol-5-yl]sulfonyl}acetate.

¹H-NMR (CDCl₃) δ: 8.26 (d, J= 2.0 Hz, 1H), 7.72 (dd, J= 8.6, 2.0 Hz, 1H), 7.41 (d, J= 8.6 Hz, 1H), 4.09 (d, J= 7.3 Hz, 2H), 4.02-3.95 (m, 2H), 3.73 (s, 3H), 3.36-3.24 (m, 2H), 2.84 (s, 2H), 2.16-2.02 (m, 1H), 1.65 (s, 6H), 1.52-1.42 (m, 4H), 1.11 (s, 9H).

MS (ESI) 451 (M + H)⁺.

10 Step G.{[2-(2,2-Dimethylpropyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]sulfonyl}-2-methylpropan-1-ol

The title compound was prepared according to the procedure described in Step H of Example 32 using methyl {[2-(2,2-dimethylpropyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]sulfonyl}-2-

- 15 methylpropanoate (Step F) instead of methyl 2-{[1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazol-5-yl]sulfonyl}-2-methylpropanoate.

¹H-NMR (CDCl₃) δ: 8.30 (d, J= 2.0 Hz, 1H), 7.77 (dd, J= 8.6, 2.0 Hz, 1H), 7.44 (d, J= 8.6 Hz, 1H), 4.11 (d, J= 7.3 Hz, 2H), 4.02-3.95 (m, 2H), 3.76 (d, J= 6.6 Hz, 2H), 3.36-3.26 (m, 2H), 2.84 (s, 2H), 2.19-2.04 (m, 1H), 1.50-1.42 (m, 4H), 1.35 (s, 6H), 1.12 (s, 9H), a peak of OH was not identified.

- 20 MS (ESI) 423 (M + H)⁺.

Step H.{[2-(2,2-Dimethylpropyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]sulfonyl}-2-methylpropan-1-ol hydrochloride

The title compound was prepared according to the procedure described in Step B of Example 27 using

- 25 {[2-(2,2-dimethylpropyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]sulfonyl}-2-methylpropan-1-ol (Step G) instead of 2-*tert*-butyl-5-(ethylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazole.

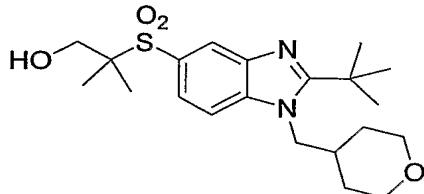
¹H-NMR (CDCl₃) δ: 8.69 (s, 1H), 7.99 (d, J= 8.6 Hz, 1H), 7.70 (s, 1H), 4.28 (d, J= 7.3 Hz, 2H), 4.02-3.98 (m, 2H), 3.79 (s, 2H), 3.38-3.28 (m, 2H), 3.24 (s, 2H), 2.30-2.05 (m, 1H), 1.55-1.45 (m, 4H), 1.35 (s, 6H),

- 30 1.20 (s, 9H), a peak of OH was not observed.

MS (ESI) 423 (M + H)⁺.

Example 372-[{2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]sulfonyl}-2-methylpropan-

- 35 1-ol and its hydrochloride salt



Step A. N-{5-Bromo-2-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}-2,2-dimethylpropanamide

The title compound was prepared according to the procedure described in Step A of Example 35 using 4-bromo-N¹-(tetrahydro-2H-pyran-4-ylmethyl)benzene-1,2-diamine (Step B of Example 36) instead of 1-{[(2-amino-4-bromophenyl)amino]methyl}cyclopentanol.

¹H-NMR (CDCl₃) δ: 7.42 (d, J= 2.9 Hz, 1H), 7.31 (br., 1H), 7.23 (dd, J= 8.8, 2.2 Hz, 1H), 6.65 (d, J= 8.8 Hz, 1H), 4.00 (dd, J= 12.5, 5.1 Hz, 2H), 3.89 (br., 1H), 3.49 (ddd, J= 11.7, 11.7, 2.2 Hz, 2H), 2.97 (t, J= 6.6 Hz, 2H), 1.90-1.80 (m, 1H), 1.74-1.64 (m, 2H), 1.47-1.35 (m, 2H), 1.34 (s, 9H).

MS (ESI) 369 (M + H)⁺.

Step B. 5-Bromo-2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole

The title compound was prepared according to the procedure described in Step D of Example 32 using N-{5-bromo-2-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}-2,2-dimethylpropanamide (Step A) instead of N-{5-bromo-2-[(cyclopropylmethyl)amino]phenyl}-3,3-dimethylbutanamide.

¹H-NMR (CDCl₃) δ: 7.88 (d, J= 1.8 Hz, 1H), 7.33 (dd, J= 8.4, 1.8 Hz, 1H), 7.20 (d, J= 8.4 Hz, 1H), 4.18 (d, J= 7.3 Hz, 2H), 4.01-3.95 (m, 2H), 3.36-3.27 (m, 2H), 2.32-2.21 (m, 1H), 1.56 (s, 9H), 1.53-1.47 (m, 4H). MS (ESI) 351(M + H)⁺.

Step C. Methyl {[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]thio}acetate

The title compound was prepared according to the procedure described in Step E of Example 32 using 5-bromo-2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole (Step B) instead of 5-bromo-1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1H-benzimidazole.

¹H-NMR (CDCl₃) δ: 7.87 (d, J= 1.3 Hz, 1H), 7.38-7.25 (m, 2H), 4.18 (d, J= 7.3 Hz, 2H), 4.01-3.95 (m, 2H), 3.71 (s, 3H), 3.63 (s, 2H), 3.45-3.27 (m, 2H), 2.33-2.22 (m, 1H), 1.66-1.48 (m, 13H).

MS (ESI) 377 (M + H)⁺.

Step D. Methyl {[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]sulfonyl}acetate

The title compound was prepared according to the procedure described in Step B of Example 1 using methyl {[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]thio}acetate (Step C) instead of 1-chloro-4-(isopropylthio)benzene.

¹H-NMR (CDCl₃) δ: 8.35 (d, J= 1.3 Hz, 1H), 7.80 (dd, J= 8.6, 1.3 Hz, 1H), 7.48 (d, J= 8.6 Hz, 1H), 4.26 (d, J= 7.9 Hz, 2H), 4.15 (s, 2H), 4.06-3.95 (m, 2H), 3.72 (s, 3H), 3.37-3.27 (m, 2H), 2.37-2.22 (m, 1H), 1.68-1.49 (m, 13H).

MS (ESI) 409 (M + H)⁺.

Step E. Methyl{[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]sulfonyl}-2-methylpropanoate

The title compound was prepared according to the procedure described in Step G of Example 32 using methyl {[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]sulfonyl}acetate (Step D) instead of methyl {[1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1H-benzimidazol-5-yl]sulfonyl}acetate.

¹H-NMR (CDCl₃) δ: 8.27 (d, J= 1.3 Hz, 1H), 7.69 (dd, J= 8.6, 1.3 Hz, 1H), 7.44 (d, J= 8.6 Hz, 1H), 4.25 (d, J= 7.3 Hz, 2H), 4.03-3.95 (m, 2H), 3.73 (s, 3H), 3.38-3.28 (m, 2H), 1.64-1.50 (m, 19H).

MS (ESI) 437 ($M + H$)⁺.

Step F.

{[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]sulfonyl}-2-methylpropan-1-ol

The title compound was prepared according to the procedure described in Step H of Example

- 5 32 using methyl {[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]sulfonyl}-2-methylpropanoate (Step E) instead of methyl 2-{[1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazol-5-yl]sulfonyl}-2-methylpropanoate.

- 10 ¹H-NMR (CDCl₃) δ: 8.30 (d, *J*= 2.0 Hz, 1H), 7.75 (dd, *J*= 8.6, 2.0 Hz, 1H), 7.48 (d, *J*= 8.6 Hz, 1H), 4.27 (d, *J*= 7.3 Hz, 2H), 4.04-3.96 (m, 2H), 3.76-3.74 (m, 2H), 3.38-3.29 (m, 2H), 3.05 (br., 1H), 2.38-2.21 (m, 1H), 1.18-1.50 (m, 13H), 1.33 (s, 6H).

MS (ESI) 409 ($M + H$)⁺.

Step G.

{[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]sulfonyl}-2-methylpropan-1-ol hydrochloride

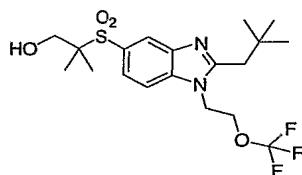
- 15 The title compound was prepared according to the procedure described in Step B of Example 27 using {[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]sulfonyl}-2-methylpropan-1-ol (Step F) instead of 2-*tert*-butyl-5-(ethylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazole.

- 20 ¹H-NMR (CDCl₃) δ: 8.14 (br., 1H), 8.08 (d, *J*= 8.6 Hz, 1H), 7.80 (dd, *J*= 8.6, 1.3 Hz, 1H), 4.46-4.43 (m, 2H), 3.85-3.81 (m, 2H), 3.52 (s, 2H), 3.24-3.16 (m, 2H), 2.22 (br., 1H), 1.58 (s, 9H), 1.55-1.39 (m, 4H), 1.21 (s, 6H).

MS (ESI) 409($M + H$)⁺.

Example 38

- 25 2-{[2-(2,2-Dimethylpropyl)-1-[2-(trifluoromethoxy)ethyl]-1*H*-benzimidazol-5-yl]sulfonyl}-2-methylpropan-1-ol



Step A. 4-Bromo-2-nitro-N-[2-(trifluoromethoxy)ethyl]aniline

The title compound was prepared according to the procedure described in Step A of Example 5

- 30 from 2-(trifluoromethoxy)ethanamine hydrochloride (J. Org. Chem. 2001, 66, 1061-1063), 4-bromo-1-fluoro-2-nitrobenzene (Wako Pure Chemical Industries, Ltd.) and *N,N*-diisopropylethylamine.

- ¹H-NMR (CDCl₃) δ: 8.36 (d, *J*= 2.2 Hz, 1H), 8.17 (br., 1H), 7.55 (dd, *J*= 8.8, 2.2 Hz, 1H), 6.79 (d, *J*= 9.5 Hz, 1H), 4.22 (t, *J*= 5.1 Hz, 2H), 3.67 (t, *J*= 5.1 Hz, 2H).

MS (ESI) 328 ($M + H$)⁺, 326 ($M - H$)⁻.

- 35 Step B. 4-Bromo-N¹-[2-(trifluoromethoxy)ethyl]benzene-1,2-diamine

The title compound was prepared according to the procedure described in step E of Example 1 using 4-bromo-2-nitro-N-[2-(trifluoromethoxy)ethyl]aniline (step A) instead of

N-(cyclopropylmethyl)-4-(isopropylsulfonyl)-2-nitroaniline.

$^1\text{H-NMR}$ (CDCl_3) δ : 6.92-6.86 (m, 2H), 6.52 (d, $J= 8.8$ Hz, 1H), 4.19 (t, $J= 5.1$ Hz, 2H), 3.60-3.34 (m, 5H).

MS (ESI) 299 ($M + H$) $^+$.

Step C. *N*-(5-Bromo-2-{{[2-(trifluoromethoxy)ethyl]amino}phenyl}-3,3-dimethylbutanamide

5 To a solution of 4-bromo- N^1 -[2-(trifluoromethoxy)ethyl]benzene-1,2-diamine (step B, 752 mg, 2.51 mmol) in ethyl acetate (22 mL) was added *tert*-butylacetyl chloride (355 mg, 2.64 mmol) at room temperature. After stirring for 2 h at room temperature, the mixture was diluted with ethyl acetate. The organic solution was washed with saturated sodium hydrogencarbonate aqueous solution, brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 4 : 1 as eluent) to afford the title compound (728 mg, 73%) as a white solid.

10 $^1\text{H-NMR}$ (CDCl_3) δ : 7.50 (d, $J= 2.6$ Hz, 1H), 7.26-7.18 (m, 2H), 6.55 (d, $J= 8.6$ Hz, 1H), 4.17-4.15 (m, 2H), 3.43-3.34 (br., 2H), 2.27 (s, 2H), 1.12 (s, 9H).

MS (ESI) 397 ($M + H$) $^+$, 395 ($M - H$) $^-$.

15 Step D. 5-Bromo-2-(2,2-dimethylpropyl)-1-[2-(trifluoromethoxy)ethyl]-1*H*-benzimidazole

A mixture of *N*-(5-bromo-2-{{[2-(trifluoromethoxy)ethyl]amino}phenyl}-3,3-dimethylbutanamide (step C, 728 mg, 1.83 mmol) and *p*-toluenesulfonic acid monohydrate (350 mg, 1.83 mmol) in toluene (20 mL) was stirred at 120°C for 8 h. Then, the mixture was allowed to cool to room temperature overnight to afford crystalline precipitates. The precipitates were collected by filtration, and dissolved in ethyl acetate and saturated sodium hydrogencarbonate aqueous solution. The organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to afford the title compound (555 mg, 80%) as an amber solid.

20 $^1\text{H-NMR}$ (CDCl_3) δ : 7.91 (d, $J= 2.2$ Hz, 1H), 7.38 (dd, $J= 8.8, 2.2$ Hz, 1H), 7.17 (d, $J= 8.8$ Hz, 1H), 4.47 (t, $J= 5.1$ Hz, 2H), 4.22 (t, $J= 5.1$ Hz, 2H), 2.80 (s, 2H), 1.09 (s, 9H).

25 MS (ESI) 379 ($M + H$) $^+$.

Step E. Methyl ({2-(2,2-dimethylpropyl)-1-[2-(trifluoromethoxy)ethyl]-1*H*-benzimidazol-5-yl}thio)acetate

The title compound was prepared according to the procedure described in step E of Example 32 using 5-bromo-2-(2,2-dimethylpropyl)-1-[2-(trifluoromethoxy)ethyl]-1*H*-benzimidazole (step D) instead of 5-bromo-1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazole.

30 $^1\text{H-NMR}$ (CDCl_3) δ : 7.89 (d, $J= 1.5$ Hz, 1H), 7.40 (dd, $J= 8.1, 1.5$ Hz, 1H), 7.23 (d, $J= 8.1$ Hz, 1H), 4.47 (t, $J= 5.9$ Hz, 2H), 4.23 (t, $J= 5.9$ Hz, 2H), 3.71 (s, 3H), 3.65 (s, 2H), 2.80 (s, 2H), 1.10 (s, 9H).

MS (ESI) 405 ($M + H$) $^+$.

Step F. Methyl ({2-(2,2-dimethylpropyl)-1-[2-(trifluoromethoxy)ethyl]-1*H*-benzimidazol-5-yl}sulfonyl)acetate

The title compound was prepared according to the procedure described in step B of Example 1 using methyl ({2-(2,2-dimethylpropyl)-1-[2-(trifluoromethoxy)ethyl]-1*H*-benzimidazol-5-yl}thio)acetate (step E) instead of 1-chloro-4-(isopropylthio)benzene.

35 $^1\text{H-NMR}$ (CDCl_3) δ : 8.38 (d, $J= 1.5$ Hz, 1H), 7.86 (dd, $J= 8.8, 1.5$ Hz, 1H), 7.46(d, $J= 8.8$ Hz, 1H), 4.56 (t, $J= 5.1$ Hz, 2H), 4.28 (t, $J= 5.1$ Hz, 2H), 4.17 (s, 2H), 3.71 (s, 3H), 2.87 (s, 2H), 1.12 (s, 9H).

MS (ESI) 437 ($M + H$) $^+$, 435 ($M - H$) $^-$.

40 Step G. Methyl

2-({2-(2,2-dimethylpropyl)-1-[2-(trifluoromethoxy)ethyl]-1H-benzimidazol-5-yl}sulfonyl)-2-methylpropanoate

The title compound was prepared according to the procedure described in step G of Example 32 using methyl ({2-(2,2-dimethylpropyl)-1-[2-(trifluoromethoxy)ethyl]-1H-benzimidazol-5-yl}sulfonyl)acetate (step F) instead of methyl {[1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1H-benzimidazol-5-yl]sulfonyl}acetate.

¹H-NMR (CDCl₃) δ: 8.28 (br., 1H), 7.55 (dd, J= 8.8, 1.5 Hz, 1H), 7.42 (d, J= 8.1 Hz, 1H), 4.55 (t, J= 5.1 Hz, 2H), 4.27 (t, J= 5.1 Hz, 2H), 3.70 (s, 3H), 2.85 (s, 2H), 1.65 (s, 6H), 1.12 (s, 9H).
MS (ESI) 465 (M + H)⁺.

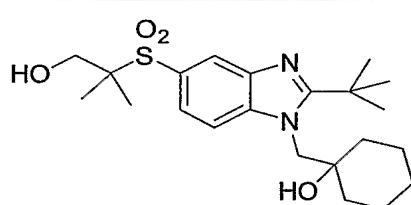
10 Step H.

2-({2-(2,2-Dimethylpropyl)-1-[2-(trifluoromethoxy)ethyl]-1H-benzimidazol-5-yl}sulfonyl)-2-methylpropan-1-ol

The title compound was prepared according to the procedure described in step H of Example 32 using methyl 2-({2-(2,2-dimethylpropyl)-1-[2-(trifluoromethoxy)ethyl]-1H-benzimidazol-5-yl}sulfonyl)-2-methylpropanoate (step G) instead of methyl 2-[(1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1H-benzimidazol-5-yl)sulfonyl]-2-methylpropanoate.
¹H-NMR (CDCl₃) δ: 8.32 (d, J= 1.5 Hz, 1H), 7.80 (dd, J= 8.1, 1.5 Hz, 1H), 7.45 (d, J= 8.8 Hz, 1H), 4.55 (t, J= 5.1 Hz, 2H), 4.28 (t, J= 5.1 Hz, 2H), 3.76 (d, J= 6.6 Hz, 2H), 3.05 (t, J= 6.6 Hz, 1H), 2.86 (s, 2H), 1.33 (s, 6H), 1.13 (s, 9H).
MS (ESI) 437 (M + H)⁺.

Example 39

1-[(2-tert-Butyl-5-[(2-hydroxy-1,1-dimethylethyl)sulfonyl]-1H-benzimidazol-1-yl)methyl]cyclohexanol and its hydrochloride salt



25

Step A. 1-[(4-Bromo-2-nitrophenyl)amino]methyl)cyclohexanol

The title compound was prepared according to the procedure described in Step A of Example 5 from 4-bromo-1-fluoro-2-nitrobenzene (Wako Pure Chemical Industries, Ltd.), 1-(aminomethyl)cyclohexanol hydrochloride (J. Med. Chem. 1981, 24, 7-12.) and 30 N,N-diisopropylethylamine.

¹H-NMR (CDCl₃) δ: 8.34 (br., 1H), 8.32 (d, J= 2.3 Hz, 1H), 7.48 (dd, J= 8.9, 2.3 Hz, 1H), 6.86 (d, J= 8.9 Hz, 1H), 3.29 (d, J= 5.9 Hz, 2H), 1.73-1.19 (m, 2H).

MS (ESI) 329 (M + H)⁺, 327 (M - H)⁻.

Step B. 1-[(2-Amino-4-bromophenyl)amino]ethyl)cyclohexanol

35 The title compound was prepared according to the procedure described in Step B of Example 32 using 1-[(4-bromo-2-nitrophenyl)amino]methyl)cyclohexanol (Step A) instead of

4-bromo-N-(cyclopropylmethyl)-2-nitroaniline.

¹H-NMR (CDCl₃) δ: 6.88 (dd, J= 8.6, 2.0 Hz, 1H), 6.82 (d, J= 2.0 Hz, 1H), 6.53 (d, J= 8.6 Hz, 1H), 3.48 (br., 3H), 3.01 (s, 2H), 1.99-1.26 (m, 1H).

MS (ESI) 299 (M + H)⁺, 297 (M - H)⁻.

5 **Step C. 1-[(5-Bromo-2-*tert*-butyl-1*H*-benzimidazol-1-yl)methyl]cyclohexanol**

To a solution of 1-[(2-amino-4-bromophenyl)amino]ethyl]cyclohexanol (Step B, 892 mg, 2.8 mmol) in toluene (15 mL) was added pivaloyl chloride (379 μL, 3.1 mmol) at room temperature. After stirring for 15 min, *p*-toluenesulfonic acid monohydrate (533mg, 2.8 mmol) was added and the mixture was stirred under reflux for 17 h with Dean-Stark apparatus. Water (5 mL) and saturated sodium

10 hydrogencarbonate aqueous solution were added and the mixture was extracted with ethyl acetate (15 mL x 3). The organic extracts were dried over sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 9 : 1 then 4 : 1 as eluent) to afford the title compound (215 mg, 21%).

¹H-NMR (CDCl₃) δ: 7.86 (d, J= 2.0 Hz, 1H), 7.54 (d, J= 8.6 Hz, 1H), 7.29 (dd, J= 8.6, 2.0 Hz, 1H), 4.38 (s, 15 2H), 1.81-1.13 (m, 20H).

MS (ESI) 365 (M + H)⁺.

Step D. Methyl ({2-*tert*-butyl-1-[(1-hydroxycyclohexyl)methyl]-1*H*-benzimidazol-5-yl}thio)acetate

The title compound was prepared according to the procedure described in Step D of Example 36 using 1-[(5-bromo-2-*tert*-butyl-1*H*-benzimidazol-1-yl)methyl]cyclohexanol (Step C) instead of 20 5-bromo-2-(2,2-dimethylpropyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazole.

¹H-NMR (CDCl₃) δ: 7.85 (d, J= 1.7 Hz, 1H), 7.58 (d, J= 8.6 Hz, 1H), 7.32 (dd, J= 8.6, 1.7 Hz, 1H), 4.38 (s, 2H), 3.71 (s, 3H), 3.64 (s, 2H), 1.72-1.43 (m, 20H).

MS (ESI) 391 (M + H)⁺, 435 (M + HCOO)⁻.

Step E. Methyl ({2-*tert*-butyl-1-[(1-hydroxycyclohexyl)methyl]-1*H*-benzimidazol-5-yl}sulfonyl)acetate

25 The title compound was prepared according to the procedure described in Step B of Example 1 using methyl ({2-*tert*-butyl-1-[(1-hydroxycyclohexyl)methyl]-1*H*-benzimidazol-5-yl}thio)acetate (Step D) instead of 1-chloro-4-(isopropylthio)benzene.

¹H-NMR (CDCl₃) δ: 8.32 (d, J= 1.3 Hz, 1H), 7.87 (d, J= 8.6 Hz, 1H), 7.76 (dd, J= 8.6, 1.3 Hz, 1H), 4.45 (s, 2H), 4.14 (s, 2H), 3.72 (s, 3H), 1.76-1.46 m, 20H).

30 MS (ESI) 423 (M + H)⁺, 421 (M - H)⁻.

Step F. Methyl ({2-*tert*-butyl-1-[(1-hydroxycyclohexyl)methyl]-1*H*-benzimidazol-5-yl}sulfonyl)-2-methylpropanoate

The title compound was prepared according to the procedure described in Step G of Example 32 using methyl ({2-*tert*-butyl-1-[(1-hydroxycyclohexyl)methyl]-1*H*-benzimidazol-5-yl}sulfonyl)acetate (Step 35 E) instead of methyl {[1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazol-5-yl]sulfonyl}acetate.

¹H-NMR (CDCl₃) δ: 8.24 (d, J= 1.3 Hz, 1H), 7.83 (d, J= 9.2 Hz, 1H), 7.64 (dd, J= 9.2, 1.3 Hz, 1H), 4.44 (2, 2H), 3.72 (s, 3H), 1.74-1.46 (m, 19H), a peak of OH was not identified.

MS (ESI) 451 (M + H)⁺, 495 (M + HCOO)⁻.

Step G. 1-({2-*tert*-Butyl-5-[(2-hydroxy-1,1-dimethylethyl)sulfonyl]-1*H*-benzimidazol-1-yl}methyl)cyclohexanol

40 cyclohexanol

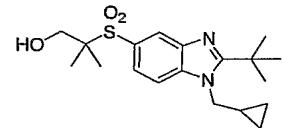
The title compound was prepared according to the procedure described in Step H of Example 32 using methyl ({2-*tert*-butyl-1-[(1-hydroxycyclohexyl)methyl]-1*H*-benzimidazol-5-yl}sulfonyl)-2-methylpropanoate (Step F) instead of methyl 5 2-{{[1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazol-5-yl]sulfonyl}-2-methylpropanoate.
¹H-NMR (CDCl₃) δ: 8.27 (d, J= 1.8 Hz, 1H), 7.87 (d, J= 8.8 Hz, 1H), 7.70 (dd, J= 8.8, 1.8 Hz, 1H), 4.45 (s, 2H), 3.74 (d, J= 6.6 Hz, 2H), 1.76-1.47 (m, 19H), 1.33 (s, 6H).
MS (ESI) 423 (M + H)⁺, 467 (M + HCOO)⁻.

Step H. 1-({2-*tert*-Butyl-5-[(2-hydroxy-1,1-dimethylethyl)sulfonyl]-1*H*-benzimidazol-1-yl}methyl)cyclohexanol hydrochloride

The title compound was prepared according to the procedure described in Step B of Example 27 using 1-({2-*tert*-butyl-5-[(2-hydroxy-1,1-dimethylethyl)sulfonyl]-1*H*-benzimidazol-1-yl}methyl)cyclohexanol (Step G) instead of 2-*tert*-butyl-5-(ethylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazole.
¹H-NMR (CDCl₃) δ: 8.13 (d, J= 8.1 Hz, 1H), 8.08 (s, 1H), 7.78 (d, J= 8.1 Hz, 1H), 4.53 (s, 2H), 3.52 (s, 2H), 15 1.62 (s, 9H), 1.57-1.37 (m, 10H), 1.22 (s, 6H).
MS (ESI) 423 (M + H)⁺, 467 (M + HCOO)⁻.

Example 40

2-{{2-*tert*-Butyl-1-(cyclopropylmethyl)-1*H*-benzimidazol-5-yl}sulfonyl}-2-methylpropan-1-ol



20

Step A. N-{{5-Bromo-2-[(cyclopropylmethyl)amino]phenyl}-2,2-dimethylpropanamide}

The title compound was prepared according to the procedure described in step A of Example 35 using 4-bromo-N¹-(cyclopropylmethyl)benzene-1,2-diamine (step B of Example 32) instead of 1-{{(2-amino-4-bromophenyl)amino}methyl}cyclopentanol.

25 ¹H-NMR (CDCl₃) δ: 7.56 (d, J= 2.2 Hz, 1H), 7.40 (br., 1H), 7.19 (dd, J= 8.8, 2.2 Hz, 1H), 6.63 (d, J= 8.1 Hz, 1H), 3.71 (br., 1H), 2.88 (d, J= 6.6 Hz, 2H), 1.34 (s, 9H), 1.12-1.03 (m, 1H), 0.58-0.52 (m, 2H), 0.26-0.21 (m, 2H).
MS (ESI) 325 (M + H)⁺, 323 (M - H)⁻.

Step B. 5-Bromo-2-*tert*-butyl-1-(cyclopropylmethyl)-1*H*-benzimidazole

30 A mixture of N-{{5-bromo-2-[(cyclopropylmethyl)amino]phenyl}-2,2-dimethylpropanamide (step A, 1.41 g, 4.34 mmol) and *p*-toluenesulfonic acid monohydrate (825 mg, 4.34 mmol) in toluene (50 mL) was stirred at 120°C for 20 h. After cooling to room temperature, the mixture was quenched with sodium hydrogencarbonate aqueous solution. The organic layer was separated. The aqueous layer was extracted with ethylacetate. The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 10 : 1 as eluent) to afford the title compound (1.40 g, quantum yield) as a light brown oil.

¹H-NMR (CDCl₃) δ: 7.89 (d, J= 2.0 Hz, 1H), 7.33 (dd, J= 8.6, 2.0 Hz, 1H), 7.23 (d, J= 8.6 Hz, 1H), 4.23 (d, J= 6.6 Hz, 2H), 1.57 (s, 9H), 1.21-1.11 (m, 1H), 0.71-0.64 (m, 2H), 0.50-0.44 (m, 2H).

MS (ESI) 307 (M + H)⁺.

Step C. Methyl {[2-*tert*-butyl-1-(cyclopropylmethyl)-1*H*-benzimidazol-5-yl]thio}acetate

5 The title compound was prepared according to the procedure described in step E of Example 32 using 5-bromo-2-*tert*-butyl-1-(cyclopropylmethyl)-1*H*-benzimidazole (step B) instead of 5-bromo-1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazole.

10 ¹H-NMR (CDCl₃) δ: 7.88 (d, J= 1.5 Hz, 1H), 7.37 (dd, J= 8.1, 1.5 Hz, 1H), 7.30 (d, J= 8.1 Hz, 1H), 4.23 (d, J= 6.6 Hz, 2H), 3.70 (s, 3H), 3.62 (s, 2H), 1.57 (s, 9H), 1.22-1.13 (m, 1H), 0.71-0.64 (m, 2H), 0.51-0.46 (m, 2H).

MS (ESI) 333 (M + H)⁺.

Step D. Methyl {[2-*tert*-butyl-1-(cyclopropylmethyl)-1*H*-benzimidazol-5-yl]sulfonyl}acetate

15 The title compound was prepared according to the procedure described in step B of Example 1 using methyl {[2-*tert*-butyl-1-(cyclopropylmethyl)-1*H*-benzimidazol-5-yl]thio}acetate (step C) instead of 1-chloro-4-(isopropylthio)benzene.

¹H-NMR (CDCl₃) δ: 8.36 (d, J= 1.3 Hz, 1H), 7.81 (dd, J= 8.6, 2.0 Hz, 1H), 7.52 (d, J= 9.2 Hz, 1H), 4.31(d, J= 6.0 Hz, 2H), 4.14 (s, 3H), 3.72 (s, 2H), 1.60 (s, 9H), 1.25-1.14 (m, 1H), 0.76-0.69 (m, 2H), 0.55-0.49 (m, 2H).

MS (ESI) 365 (M + H)⁺, 363 (M - H)⁻.

20 Step E. Methyl 2-{[2-*tert*-butyl-1-(cyclopropylmethyl)-1*H*-benzimidazol-5-yl]sulfonyl}-2-methylpropanoate

The title compound was prepared according to the procedure described in step G of Example 32 using methyl {[2-*tert*-butyl-1-(cyclopropylmethyl)-1*H*-benzimidazol-5-yl]sulfonyl}acetate (step D) instead of methyl {[1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazol-5-yl]sulfonyl}acetate.

25 ¹H-NMR (CDCl₃) δ: 8.28 (d, J= 2.0 Hz, 1H), 7.69 (dd, J= 8.6, 2.0 Hz, 1H), 7.48 (d, J= 8.6 Hz, 1H), 4.30 (d, J= 6.6 Hz, 2H), 3.73 (s, 3H), 1.63 (s, 6H), 1.60 (s, 9H), 1.25-1.13 (m, 1H), 0.76-0.69 (m, 2H), 0.55-0.49 (m, 2H).

MS (ESI) 393 (M + H)⁺.

Step F. 2-{[2-*tert*-Butyl-1-(cyclopropylmethyl)-1*H*-benzimidazol-5-yl]sulfonyl}-2-methylpropan-1-ol

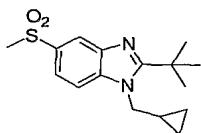
30 The title compound was prepared according to the procedure described in step H of Example 32 using methyl 2-{[2-*tert*-butyl-1-(cyclopropylmethyl)-1*H*-benzimidazol-5-yl]sulfonyl}-2-methylpropanoate (step E) instead of methyl 2-{[1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazol-5-yl]sulfonyl}-2-methylpropanoate.

35 ¹H-NMR (CDCl₃) δ: 8.31 (d, J= 1.5 Hz, 1H), 7.75 (dd, J= 8.8, 1.5 Hz, 1H), 7.52 (d, J= 8.8 Hz, 1H), 4.32 (d, J= 6.6 Hz, 2H), 3.74 (d, J= 6.6 Hz, 2H), 3.08 (t, J= 6.6 Hz, 1H), 1.61 (s, 9H), 1.32 (s, 6H), 1.28-1.14 (m, 1H), 0.76-0.70 (m, 2H), 0.55-0.50 (m, 2H).

MS (ESI) 365 (M + H)⁺.

Example 41

40 2-*tert*-Butyl-1-(cyclopropylmethyl)-5-(methylsulfonyl)-1*H*-benzimidazole



Step A. *N*-[2-[(Cyclopropylmethyl)amino]-5-(methylsulfonyl)phenyl]-2,2-dimethylpropanamide

The title compound was prepared according to the procedure described in step A of Example 31 using 2-amino-1-(*N*-cyclopropylmethylamino)-4-(methylsulfonyl)benzene (step B of Example 4) instead of 4-(ethylsulfonyl)-*N*¹-[2-(trifluoromethoxy)ethyl]benzene-1,2-diamine.

¹H-NMR (CDCl₃) δ: 7.68-7.63 (m, 2H), 7.38 (br., 1H), 6.78 (d, *J*= 8.6 Hz, 1H), 3.04 (d, *J*= 7.3 Hz, 2H), 3.01 (s, 3H), 1.37 (s, 9H), 1.20-1.07 (m, 1H), 0.62-0.55 (m, 2H), 0.32-0.27 (m, 2H), a peak of NH was not identified.

MS (ESI) 325 (M + H)⁺, 323 (M - H)⁻.

10 Step B. 2-*tert*-Butyl-1-(cyclopropylmethyl)-5-(methylsulfonyl)-1*H*-benzimidazole

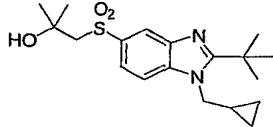
The title compound was prepared according to the procedure described in step B of Example 31 using *N*-[2-[(cyclopropylmethyl)amino]-5-(methylsulfonyl)phenyl]-2,2-dimethylpropanamide (step A) instead of *N*-(5-(Ethylsulfonyl)-2-[(2-(trifluoromethoxy)ethyl)amino]phenyl)-2,2-dimethylpropanamide.

¹H-NMR (CDCl₃) δ: 8.37 (d, *J*= 1.5 Hz, 1H), 7.82 (dd, *J*= 8.8, 1.5 Hz, 1H), 7.51 (d, *J*= 8.8 Hz, 1H), 4.32 (d, *J*= 5.9 Hz, 2H), 3.07 (s, 3H), 1.60 (s, 9H), 1.24-1.11 (m, 1H), 0.75-0.68 (m, 2H), 0.55-0.49 (m, 2H).

MS (ESI) 307 (M + H)⁺.

Example 42

1-[[2-*tert*-Butyl-1-(cyclopropylmethyl)-1*H*-benzimidazol-5-yl]sulfonyl]-2-methylpropan-2-ol



20

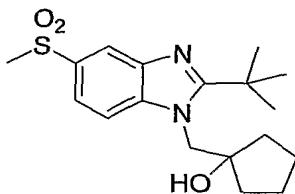
The title compound was prepared according to the procedure described in Example 33 using 2-*tert*-butyl-1-(cyclopropylmethyl)-5-(methylsulfonyl)-1*H*-benzimidazole (Example 41) instead of 1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-(methylsulfonyl)-1*H*-benzimidazole.

¹H-NMR (CDCl₃) δ: 8.34 (d, *J*= 1.5 Hz, 1H), 7.79 (dd, *J*= 8.8, 1.5 Hz, 1H), 7.51 (d, *J*= 8.8 Hz, 1H), 4.31 (d, *J*= 6.6 Hz, 2H), 3.85 (s, 1H), 3.34 (s, 2H), 1.60 (s, 9H), 1.43 (s, 6H), 1.25-1.12 (m, 1H), 0.75-0.68 (m, 2H), 0.54-0.49 (m, 2H).

MS (ESI) 365 (M + H)⁺.

Example 43

30 1-[[2-*tert*-Butyl-5-(methylsulfonyl)-1*H*-benzimidazol-1-yl]methyl]cyclopentanol



Step A. 1-({[4-(Methylsulfonyl)-2-nitrophenyl]amino}methyl)cyclopentanol

The title compound was prepared according to the procedure described in Step A of Example 5 from 1-fluoro-4-(methylsulfonyl)-2-nitrobenzene (Acros Organics) and 1-(aminomethyl)cyclopentanol

5 hydrochloride (*J. Med. Chem.* 1981, 24, 7-12).

$^1\text{H-NMR}$ (CDCl_3) δ : 8.79 (br, 1H), 8.76 (d, $J=2.0$ Hz, 1H), 7.87 (dd, $J=9.2, 2.0$ Hz, 1H), 7.03 (d, $J=9.2$ Hz, 1H), 3.47 (d, $J=5.3$ Hz, 2H), 3.06 (s, 3H), 1.92-1.73 (m, 9H).

MS (ESI) 315 ($M + H$) $^+$, 313 ($M - H$) $^-$

Step B. 1-({[2-Amino-4-(methylsulfonyl)phenyl]amino}methyl)cyclopentanol

10 The title compound was prepared according to the procedure described in Step E of Example 1 using 1-({[4-(methylsulfonyl)-2-nitrophenyl]amino}methyl)cyclopentanol (Step A) instead of *N*-(cyclopropylmethyl)-4-(isopropylsulfonyl)-2-nitroaniline.

$^1\text{H-NMR}$ (CDCl_3) δ : 7.40 (dd, $J=8.6, 2.0$ Hz, 1H), 7.23 (d, $J=2.0$ Hz, 1H), 6.69 (d, $J=8.6$ Hz, 1H), 4.44 (br. 1H), 3.46 (br. 2H), 3.25 (d, $J=5.9$ Hz, 2H), 3.00 (s, 3H), 1.95-1.65 (m, 9H).

15 MS (ESI) 285($M + H$) $^+$, 283 ($M - H$) $^-$

Step C. N-[2-{[(1-Hydroxycyclopentyl)methyl]amino}-5-(methylsulfonyl)phenyl]-2,2-dimethylpropanamide

The title compound was prepared according to the procedure described in Step A of Example 31 using 1-({[2-amino-4-(methylsulfonyl)phenyl]amino}methyl)cyclopentanol (Step B) instead of 20 4-(ethylsulfonyl)-*N*¹-[2-(trifluoromethoxy)ethyl]benzene-1,2-diamine.

$^1\text{H-NMR}$ (CDCl_3) δ : 7.62 (dd, $J=8.6, 2.0$ Hz, 1H), 7.54 (d, $J=2.0$ Hz, 1H), 7.37 (br., 1H), 6.75 (d, $J=8.6$ Hz, 1H), 4.79 (br, 1H), 3.28 (d, $J=5.3$ Hz, 2H), 3.01 (s, 3H), 1.93-1.63 (m, 9H), 1.36 (s, 9H).

MS (ESI) 369 ($M + H$) $^+$, 367 ($M - H$) $^-$.

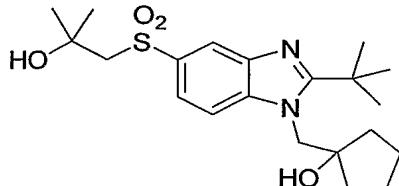
Step D. 1-{{2-tert-Butyl-5-(methylsulfonyl)-1*H*-benzimidazol-1-yl}methyl)cyclopentanol

25 The title compound was prepared according to the procedure described in Step B of Example 31 using *N*-[2-{[(1-hydroxycyclopentyl)methyl]amino}-5-(methylsulfonyl)phenyl]-2,2-dimethylpropanamide (Step C) instead of

of 4-(ethylsulfonyl)-2-{[(2-(trifluoromethoxy)ethyl)amino]phenyl}-2,2-dimethylpropanamide.

$^1\text{H-NMR}$ (CDCl_3) δ : 8.32 (s 1H), 7.76 (s, 2H), 4.63 (s, 2H), 3.05 (s, 3H), 1.91-1.69 (m, 8H), 1.59 (s, 9H), a 30 peak of OH was not identified.

MS (ESI) 351 ($M + H$) $^+$, 395 ($M + \text{HCOO}$) $^-$.

Example 441-{{2-tert-Butyl-5-[(2-hydroxy-2-methylpropyl)sulfonyl]-1*H*-benzimidazol-1-yl}methyl)cyclopentanoland its hydrochloride salt

Step A. 1-(2-tert-Butyl-5-[(2-hydroxy-2-methylpropyl)sulfonyl]-1H-benzimidazol-1-yl)methyl]cyclopentanol

The title compound was prepared according to the procedure described in Example 33 using 1-[(2-*tert*-butyl-5-(methylsulfonyl)-1*H*-benzimidazol-1-yl)methyl]cyclopentanol (Example 43) instead of 5 1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-(methylsulfonyl)-1*H*-benzimidazole.

¹H-NMR (CDCl₃) δ: 8.33 (s 1H), 7.77 (s, 2H), 4.64 (s, 2H), 3.34 (s, 2H), 1.86-1.69 (m, 8H), 1.60 (s, 9H), 1.44 (s, 6H), peaks of OH were not identified.

MS (ESI) 409 (M + H)⁺, 453 (M + HCOO)⁻.

Step B. 1-(2-tert-Butyl-5-[(2-hydroxy-2-methylpropyl)sulfonyl]-1H-benzimidazol-1-yl)methyl]cyclopentanol hydrochloride

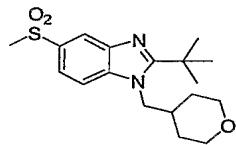
The title compound was prepared according to the procedure described in Step B of Example 27 using 1-[(2-*tert*-butyl-5-[(2-hydroxy-2-methylpropyl)sulfonyl]-1*H*-benzimidazol-1-yl)methyl]cyclopentanol (Step A) instead of 2-*tert*-butyl-5-(ethylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazole.

15 ¹H-NMR (DMSO-d₆) δ: 8.21 (s 1H), 8.17 (d, J = 8.9 Hz, 1H), 7.92 (d, J = 8.9 Hz, 1H), 4.76 (s, 2H), 3.51 (s, 2H), 1.77-1.44 (m, 17H), 1.78 (s, 6H), peaks of OH were not identified.

MS (ESI) 409 (M + H)⁺, 453 (M + HCOO)⁻.

Example 45

2-tert-Butyl-5-(methylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazole



Step A. 4-(Methylsulfonyl)-2-nitro-N-(tetrahydro-2*H*-pyran-4-ylmethyl)aniline

The title compound was prepared according to the procedure described in Step A of Example 5 from 1-fluoro-4-(methylsulfonyl)-2-nitrobenzene (Acros Organics Ltd.) and 4-aminomethyltetrahydropyran 25 (Apollo Scientific Ltd.).

¹H-NMR (CDCl₃) δ: 8.79 (d, J = 2.2 Hz, 1H), 8.54 (br., 1H), 7.91 (dd, J = 8.8, 2.2 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 4.07-4.02 (m, 2H), 3.48-3.39(m, 2H), 3.32-3.28 (m, 2H), 3.07 (s, 3H), 2.07-1.92 (m, 1H), 1.81-1.72 (m, 2H), 1.52-1.39 (m, 2H).

MS (ESI) 315 (M + H)⁺, 313 (M - H)⁻.

Step B. 4-(Methylsulfonyl)-N¹-(tetrahydro-2*H*-pyran-4-ylmethyl)benzene-1,2-diamine

The title compound was prepared according to the procedure described in step E of Example 1 using 4-(methylsulfonyl)-2-nitro-N-(tetrahydro-2*H*-pyran-4-ylmethyl)aniline (step A) instead of N-(cyclopropylmethyl)-4-(isopropylsulfonyl)-2-nitroaniline.

1¹H-NMR (CDCl₃) δ: 7.42 (dd, J = 7.9, 2.0 Hz, 1H), 7.25 (d, J = 2.0 Hz, 1H), 6.66 (d, J = 8.6 Hz, 1H), 4.12 (br., 1H), 4.05-3.99 (m, 2H), 3.46-3.37 (m, 2H), 3.36 (br., 2H), 3.11 (t, J = 6.6 Hz, 2H), 3.00 (s, 3H), 1.98-1.83 (m, 1H), 1.79-1.69 (m, 2H), 1.49-1.34 (m, 2H).

MS (ESI) 285 (M + H)⁺, 283 (M - H)⁻.

Step C. 2,2-Dimethyl-N-{5-(methylsulfonyl)-2-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}propanamide

The title compound was prepared according to the procedure described in step A of Example 31 using 4-(methylsulfonyl)-N¹-(tetrahydro-2H-pyran-4-ylmethyl)benzene-1,2-diamine (step B) instead of 5 4-(ethylsulfonyl)-N¹-[2-(trifluoromethoxy)ethyl]benzene-1,2-diamine.

¹H-NMR (CDCl₃) δ: 7.68 (dd, J= 8.6, 2.0 Hz, 1H), 7.56 (d, J= 2.0 Hz, 1H), 7.32 (br., 1H), 6.76 (d, J= 9.2 Hz, 1H), 4.04-3.98 (m, 2H), 3.45-3.35 (m, 2H), 3.10 (d, J= 6.6 Hz, 2H), 3.01 (s, 3H), 1.96-1.80 (m, 1H), 1.73-1.68 (m, 2H), 1.47-1.30 (m, 2H), 1.36 (s, 9H), a peak of NH was not identified.

MS (ESI) 369 (M + H)⁺, 367 (M - H)⁻.

10 Step D. 2-*tert*-Butyl-5-(methylsulfonyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1*H*-benzimidazole

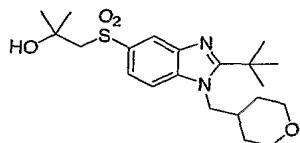
The title compound was prepared according to the procedure described in step B of Example 31 using 2,2-dimethyl-N-{5-(methylsulfonyl)-2-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}propanamide (step C) instead of N-(5-(Ethylsulfonyl)-2-[(2-(trifluoromethoxy)ethyl)amino]phenyl)-2,2-dimethylpropanamide.

15 ¹H-NMR (CDCl₃) δ: 8.36 (d, J= 2.0 Hz, 1H), 7.82 (dd, J= 8.6, 2.0 Hz, 1H), 7.48 (d, J= 8.6 Hz, 1H), 4.27 (d, J= 7.9 Hz, 2H), 4.04-3.96 (m, 2H), 3.37-3.27 (m, 2H), 3.07 (s, 3H), 2.37-2.21 (m, 1H), 1.59 (s, 9H), 1.54-1.49 (m, 4H).

MS (ESI) 351 (M + H)⁺.

20 Example 46

1-[2-*tert*-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]sulfonyl]-2-methylpropan-2-ol



The title compound was prepared according to the procedure described in Example 33 using

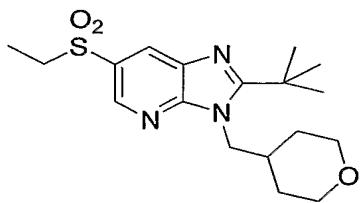
25 2-*tert*-butyl-5-(methylsulfonyl)-1-(tetrahydro-2H-pyran-4-ylmethyl)-1*H*-benzimidazole (Example 45) instead of 1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-(methylsulfonyl)-1*H*-benzimidazole.

¹H-NMR (CDCl₃) δ: 8.34 (d, J= 2.0 Hz, 1H), 7.79 (dd, J= 8.6, 2.0 Hz, 1H), 7.48 (d, J= 8.6 Hz, 1H), 4.26 (d, J= 7.9 Hz, 2H), 4.05-3.94 (m, 2H), 3.81 (s, 1H), 3.36-3.27 (m, 2H), 3.34 (s, 2H), 2.37-2.20 (m, 1H), 1.59 (s, 9H), 1.53-1.48 (m, 4H), 1.44 (s, 6H).

30 MS (ESI) 409 (M + H)⁺.

Example 47

2-*tert*-Butyl-6-(ethylsulfonyl)-3-(tetrahydro-2H-pyran-4-ylmethyl)-3*H*-imidazo[4,5-b]pyridine and its hydrochloride salt

Step A. 5-Bromo-3-nitropyridin-2(1H)-one

To a solution of 5-bromopyridin-2(1H)-one (Aldrich, 3.0g, 17.2 mmol) in sulfuric acid (18 mL) was added nitric acid (60-61%, Wako Pure Chemical Industries, Ltd., 6 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 3 h. The mixture was poured into ice water and obtained precipitate was collected by filtration. The solid was washed with water and dried in vacuo to afford the title compound (2.5 g, 68%) as a yellow solid.

¹H-NMR (CDCl₃) δ: 13.21 (br., 1H), 8.55 (d, J= 2.6 Hz, 1H), 8.19 (d, J= 2.6 Hz, 1H).

10 MS (ESI) 217 (M - H)⁻.

Step B. 5-Bromo-2-chloro-3-nitropyridine

A mixture of 5-bromo-3-nitropyridin-2(1H)-one (Step A, 2.5 g, 10.4 mmol), phosphoryl chloride (25 mL) and N,N-dimethylformamide (2.5 mL) was stirred under reflux for 3 h. After removal of solvent, the residue was dissolved in water (20 mL) and diethylether (20 mL) at 0 °C and the solution was separated. The organic layer was washed with saturated sodium hydrogen carbonate, dried over sodium sulfate and concentrated to afford the title compound (2.5 g, 89%) as a pale yellow solid.

¹H-NMR (CDCl₃) δ: 8.70 (d, J= 1.7 Hz, 1H), 8.37 (d, J= 1.7 Hz, 1H).

Step C. 5-Bromo-3-nitro-N-(tetrahydro-2H-pyran-4-ylmethyl)pyridin-2-amine

The title compound was prepared according to the procedure described in Step A of Example 5 from 5-bromo-2-chloro-3-nitropyridine (Step B), 4-aminomethyltetrahydropyran (Apollo Scientific Ltd.) and triethylamine.

¹H-NMR (CDCl₃) δ: 8.54 (d, J= 2.2 Hz, 1H), 8.43 (d, J= 2.9 Hz, 1H), 8.30 (br s, 1H), 4.04-3.96 (m, 2H), 3.54 (t, J= 6.6 Hz, 2H), 3.45-3.34 (m, 2H), 2.02-1.85 (m, 1H), 1.74-1.65 (m, 2H), 1.48-1.33 (m, 2H).

MS (ESI) 316 (M+H)⁺, 314 (M - H)⁻.

Step D. 5-Bromo-N²-(tetrahydro-2H-pyran-4-ylmethyl)pyridine-2,3-diamine

A mixture of 5-bromo-3-nitro-N-(tetrahydro-2H-pyran-4-ylmethyl)pyridin-2-amine (Step C, 792 mg, 2.51 mmol) and 3% platinum on sulfide carbon (N.E.CHEMCAT, 125 mg) in methanol (9 mL) and tetrahydrofuran (9 mL) was stirred at room temperature for 3 h under hydrogen. The mixture was filtered through a pad of celite and the filtrate was concentrated to afford the crude title compound (764 mg) as red viscous oil.

¹H-NMR (CDCl₃) δ: 7.76 (d, J= 2.2 Hz, 1H), 6.97 (d, J= 2.2 Hz, 1H), 4.19 (br s, 1H), 4.04-3.95 (m, 2H), 3.45-3.34 (m, 2H), 3.32 (t, J= 6.6 Hz, 2H), 3.20 (br s, 2H), 1.97-1.83 (m, 1H), 1.75-1.66 (m, 2H), 1.46-1.30 (m, 2H).

MS (ESI) 286 (M+H)⁺.

Step E. N-[5-Bromo-2-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl]-2,2-dimethylpropanamide

The title compound was prepared according to the procedure described in Step A of Example 35

using 5-bromo-*N*²-(tetrahydro-2*H*-pyran-4-ylmethyl)pyridine-2,3-diamine (Step D) instead of 1-[(2-amino-4-bromophenyl)amino]methyl)cyclopentanol.

¹H-NMR (CDCl₃) δ:8.09 (d, J= 2.2 Hz, 1H), 7.49 (d, J= 2.2 Hz, 1H), 7.01 (br s, 1H), 4.66 (br s, 1H), 4.03-3.95 (m, 2H), 3.44-3.34 (m, 2H), 3.31 (t, J= 6.6 Hz, 2H), 1.94-1.80 (m, 1H), 1.71-1.63 (m, 2H),

5 1.44-1.28 (m, 2H), 1.34 (s, 9H).

MS (ESI) 370 (M+H)⁺, 368 (M - H)⁻.

Step F. 6-Bromo-2-*tert*-butyl-3-(tetrahydro-2*H*-pyran-4-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine

The title compound was prepared according to the procedure described in Step B of Example

31 using *N*-{5-bromo-2-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]pyridin-3-yl}-2,2-dimethylpropanamide

10 (Step E) instead of *N*-(5-ethylsulfonyl)-2-[[2-(trifluoromethoxy)ethyl]amino]phenyl)-2,2-dimethylpropanamide.

¹H-NMR (CDCl₃) δ:8.34 (d, J= 2.0 Hz, 1H), 8.10 (d, J= 2.0 Hz, 1H), 4.31 (d, J= 7.3 Hz, 2H), 4.01-3.92 (m, 2H), 3.38-3.27 (m, 2H), 2.65-2.47 (m, 1H), 1.56 (s, 9H), 1.54-1.38 (m, 4H).

MS (ESI) 352 (M+H)⁺

15 Step G. 2-*tert*-Butyl-6-(ethylthio)-3-(tetrahydro-2*H*-pyran-4-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine

The title compound was prepared according to the procedure described in Step E of Example 32 from 6-bromo-2-*tert*-butyl-3-(tetrahydro-2*H*-pyran-4-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine (Step F) and ethanethiol (Wako Pure Chemical Industries, Ltd.).

¹H-NMR (CDCl₃) δ:8.37 (d, J= 1.5 Hz, 1H), 8.07 (d, J= 1.5 Hz, 1H), 4.32 (d, J= 8.1 Hz, 2H), 4.01-3.93 (m, 2H), 3.39-3.28 (m, 2H), 2.88 (dd, J= 7.3 Hz, 2H), 2.68-2.52 (m, 1H), 1.57 (s, 9H), 1.61-1.42 (m, 4H), 1.27 (t, J= 7.3 Hz, 3H).

MS (ESI) 334 (M+H)⁺.

Step H. 2-*tert*-Butyl-6-(ethylsulfonyl)-3-(tetrahydro-2*H*-pyran-4-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine

The title compound was prepared according to the procedure described in Step B of Example 1

25 using 2-*tert*-butyl-6-(ethylthio)-3-(tetrahydro-2*H*-pyran-4-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine (Step G) instead of 1-chloro-4-(isopropylthio)benzene.

¹H-NMR (CDCl₃) δ:8.82 (d, J= 2.2 Hz, 1H), 8.46 (d, J= 1.5 Hz, 1H), 4.39 (d, J= 7.3 Hz, 2H), 4.02-3.94 (m, 2H), 3.39-3.29 (m, 2H), 3.18 (q, J= 7.3 Hz, 2H), 2.66-2.51 (m, 1H), 1.59 (s, 9H), 1.62-1.39 (m, 4H), 1.31 (t, J= 7.3Hz, 3H).

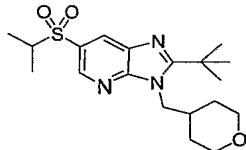
30 MS (ESI) 366 (M+H)⁺.

Step I. 2-*tert*-Butyl-6-(ethylsulfonyl)-3-(tetrahydro-2*H*-pyran-4-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine hydrochloride

The title compound was prepared according to the procedure described in Step B of Example 27 using 2-*tert*-butyl-6-(ethylsulfonyl)-3-(tetrahydro-2*H*-pyran-4-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine (Step H) instead of 2-*tert*-butyl-5-(ethylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazole.

¹H-NMR (CDCl₃) δ:8.87 (d, J= 1.5 Hz, 1H), 8.56 (d, J= 1.5 Hz, 1H), 4.41 (d, J= 7.3 Hz, 2H), 4.03-3.94 (m, 2H), 3.39-3.29 (m, 2H), 3.19 (q, J= 7.3Hz, 2H), 2.66-2.49 (m, 1H), 1.63 (s, 9H), 1.59-1.40 (m, 4H), 1.32 (t, J= 7.3Hz, 3H).

MS (ESI) 366 (M+H)⁺.

Example 48**2-*tert*-Butyl-6-(isopropylsulfonyl)-3-(tetrahydro-2*H*-pyran-4-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine and its hydrochloride salt**

5

Step A. 2-*tert*-Butyl-6-(isopropylthio)-3-(tetrahydro-2*H*-pyran-4-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine

The title compound was prepared according to the procedure described in Step E of Example 32 from 6-bromo-2-*tert*-butyl-3-(tetrahydro-2*H*-pyran-4-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine (Step F of Example 47) and 2-propanethiol (TCI Tokyo Kasei Kogyo Co., Ltd.).

- 10 ¹H-NMR (CDCl₃) δ:8.40 (br s, 1H), 8.11 (br s, 1H), 4.32 (d, J= 7.3 Hz, 2H), 4.02-3.92 (m, 2H), 3.40-3.28 (m, 2H), 3.28-3.17 (m, 1H), 2.68-2.50 (m, 1H), 1.57 (s, 9H), 1.56-1.40 (m, 4H), 1.26 (t, J= 6.6 Hz, 6H).
MS (ESI) 348 (M+H)⁺.

Step B. 2-*tert*-Butyl-6-(isopropylsulfonyl)-3-(tetrahydro-2*H*-pyran-4-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine

- 15 The title compound was prepared according to the procedure described in Step B of Example 1 using 2-*tert*-butyl-6-(isopropylthio)-3-(tetrahydro-2*H*-pyran-4-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine (Step A) instead of 1-chloro-4-(isopropylthio)benzene.

¹H-NMR (CDCl₃) δ:8.79 (d, J= 1.5Hz, 1H), 8.44 (d, J= 2.2Hz, 1H), 4.38 (d, J= 7.3Hz, 2H), 4.02-3.94 (m, 2H), 3.39-3.28 (m, 2H), 3.23 (q, J= 7.3Hz, 1H), 2.67-2.51 (m, 1H), 1.59 (s, 9H), 1.58-1.40 (m, 4H), 1.33 (t, J= 7.3 Hz, 6H).

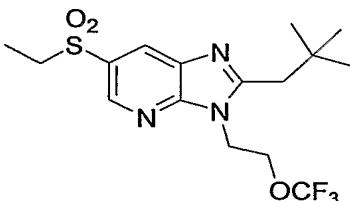
- 20 MS (ESI) 380 (M+H)⁺.

Step C. 2-*tert*-Butyl-6-(isopropylsulfonyl)-3-(tetrahydro-2*H*-pyran-4-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine hydrochloride

- 25 The title compound was prepared according to the procedure described in Step B of Example 27 using 2-*tert*-butyl-6-(isopropylsulfonyl)-3-(tetrahydro-2*H*-pyran-4-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine (Step B) instead of 2-*tert*-butyl-5-(ethylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazole.

¹H-NMR (CDCl₃) δ:8.84 (s, 1H), 8.57 (br s, 1H), 4.42 (d, J= 6.6Hz, 2H), 4.03-3.94 (m, 2H), 3.41-3.19 (m, 3H), 2.66-2.49 (m, 1H), 1.64 (s, 9H), 1.60-1.40 (m, 4H), 1.34 (t, J= 5.9 Hz, 6H).
MS (ESI) 380 (M+H)⁺.

- 30 **Example 49**

2-(2,2-Dimethylpropyl)-6-(ethylsulfonyl)-3-[2-(trifluoromethoxy)ethyl]-3*H*-imidazo[4,5-*b*]pyridine and its hydrochloride salt

Step A. 5-Bromo-3-nitro-N-[2-(trifluoromethoxy)ethyl]pyridin-2-amine

The title compound was prepared according to the procedure described in Step A of Example 5 from 5-bromo-2-chloro-3-nitropyridine (Step B of Example 47), 2-(trifluoromethoxy)ethanamine hydrochloride (*J. Org. Chem.* **2001**, 66, 1061-1063) and *N,N*-diisopropylethylamine.

- 5 $^1\text{H-NMR}$ (CDCl_3) δ : 8.58 (d, $J=2.6$ Hz, 1H), 8.45 (d, $J=2.6$ Hz, 1H), 8.33 (br., 1H), 4.20 (t, $J=5.3$ Hz, 2H), 3.99-3.93 (m, 2H).

MS (ESI) 330 ($\text{M} + \text{H}$) $^+$.

Step B. 5-Bromo- N^2 -[2-(trifluoromethoxy)ethyl]pyridine-2,3-diamine

The title compound was prepared according to the procedure described in Step D of Example

- 10 47 using 5-bromo-3-nitro-N-[2-(trifluoromethoxy)ethyl]pyridin-2-amine (Step A) instead of 5-bromo-3-nitro-*N*-(tetrahydro-2*H*-pyran-4ylmethyl)pyridin-2-amine.

$^1\text{H-NMR}$ (CDCl_3) δ : 7.75 (d, $J=2.0$ Hz, 1H), 7.01 (d, $J=2.0$ Hz, 1H), 4.19 (t, $J=5.3$ Hz, 2H), 3.82-3.71 (m, 2H), peaks of NH_2 and NH were not identified.

MS (ESI) 300 ($\text{M} + \text{H}$) $^+$.

- 15 Step C. *N*-(5-Bromo-2-[(2-(trifluoromethoxy)ethyl]amino)pyridin-3-yl)-3,3-dimethylbutanamide

The title compound was prepared according to the procedure described in Step A of Example 35 from 5-bromo- N^2 -[2-(trifluoromethoxy)ethyl]pyridine-2,3-diamine (Step B) and *tert*-butylacetyl chloride.

$^1\text{H-NMR}$ (CDCl_3) δ : 8.08 (d, $J=2.0$ Hz, 1H), 7.60 (br., 1H), 6.77 (br., 1H), 4.92 (br., 1H), 5.27 (t, $J=5.3$ Hz, 2H), 3.80-3.72 (m, 2H), 2.28 (s, 2H), 1.13 (s, 9H).

- 20 MS (ESI) 398 ($\text{M} + \text{H}$) $^+$, 396 ($\text{M} - \text{H}$) $^-$

Step D. 6-Bromo-2-(2,2-dimethylpropyl)-3-[2-(trifluoromethoxy)ethyl]-3*H*-imidazo[4,5-*b*]pyridine

The title compound was prepared according to the procedure described in Step D of Example 32 using *N*-(5-bromo-2-[(2-(trifluoromethoxy)ethyl]amino)pyridin-3-yl)-3,3-dimethylbutanamide (Step C) instead of *N*-(5-bromo-2-[(cyclopropylmethyl)amino]phenyl)-3,3-dimethylbutanamide.

- 25 $^1\text{H-NMR}$ (CDCl_3) δ : 8.35 (d, $J=2.0$ Hz, 1H), 8.14 (d, $J=2.0$ Hz, 1H), 4.58 (t, $J=5.3$ Hz, 2H), 4.36 (t, $J=5.3$ Hz, 2H), 2.85 (s, 2H), 1.10 (s, 9H).

MS (ESI) 380 ($\text{M} + \text{H}$) $^+$.

Step E. 2-(2,2-Dimethylpropyl)-6-(ethylthio)-3-[2-(trifluoromethoxy)ethyl]-3*H*-imidazo[4,5-*b*]pyridine

The title compound was prepared according to the procedure described in Step E of Example 32

- 30 from 6-bromo-2-(2,2-dimethylpropyl)-3-[2-(trifluoromethoxy)ethyl]-3*H*-imidazo[4,5-*b*]pyridine (Step D) and ethanethiol (Wako Pure Chemical Industries, Ltd.).

$^1\text{H-NMR}$ (CDCl_3) δ : 8.38-8.37 (m, 1H), 8.10-8.09 (m, 1H), 4.59 (t, $J=5.3$ Hz, 2H), 4.37 (t, $J=5.3$ Hz, 2H), 2.91 (d, $J=7.3$ Hz, 2H), 2.86 (s, 2H), 1.29 (t, $J=7.3$ Hz, 3H), 1.11 (s, 9H).

MS (ESI) 362 ($\text{M} + \text{H}$) $^+$.

- 35 Step F. 2-(2,2-Dimethylpropyl)-6-(ethylsulfonyl)-3-[2-(trifluoromethoxy)ethyl]-3*H*-imidazo[4,5-*b*]pyridine

The title compound was prepared according to the procedure described in Step B of Example 1 using 2-(2,2-dimethylpropyl)-6-(ethylthio)-3-[2-(trifluoromethoxy)ethyl]-3*H*-imidazo[4,5-*b*]pyridine (Step E) instead of 1-chloro-4-(isopropylthio)benzene.

- 40 $^1\text{H-NMR}$ (CDCl_3) δ : 8.84 (d, $J=2.0$ Hz, 1H), 8.49 (d, $J=2.0$ Hz, 1H), 4.66 (t, $J=5.3$ Hz, 2H), 4.40 (t, $J=5.3$ Hz, 2H), 3.21 (q, $J=7.3$ Hz, 2H), 2.91 (s, 2H), 1.34 (t, $J=7.3$ Hz, 3H), 1.14 (s, 9H).

MS (ESI) 394 ($M + H$)⁺.

Step G. 2-(2,2-Dimethylpropyl)-6-(ethylsulfonyl)-3-[2-(trifluoromethoxy)ethyl]-3H-imidazo[4,5-b]pyridine hydrochloride

The title compound was prepared according to the procedure described in Step B of Example

5 27 using 2-(2,2-dimethylpropyl)-6-(ethylsulfonyl)-3-[2-(trifluoromethoxy)ethyl]-3H-imidazo[4,5-b]pyridine (Step F) instead of 2-*tert*-butyl-5-(ethylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazole.

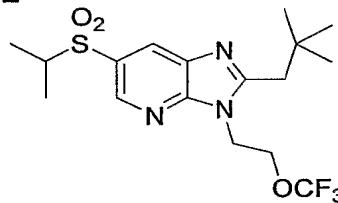
¹H-NMR (CDCl₃) δ: 9.07 (br., 1H), 8.93 (br., 1H), 4.84 (br., 2H), 4.51 (br., 2H), 3.30-3.21 (m, 4H), 1.36 (br., 3H), 1.23 (s, 9H).

MS (ESI) 394 ($M + H$)⁺.

10

Example 50

2-(2,2-Dimethylpropyl)-6-(isopropylsulfonyl)-3-[2-(trifluoromethoxy)ethyl]-3H-imidazo[4,5-b]pyridine



15

Step A. 2-(2,2-Dimethylpropyl)-6-(isopropylthio)-3-[2-(trifluoromethoxy)ethyl]-3H-imidazo[4,5-b]pyridine

The title compound was prepared according to the procedure described in Step E of Example 32 from 6-bromo-2-(2,2-dimethylpropyl)-3-[2-(trifluoromethoxy)ethyl]-3H-imidazo[4,5-b]pyridine (Step D of Example 49) and 2-propanethiol (TCI Tokyo Kasei Kogyo Co., Ltd.).

20 ¹H-NMR (CDCl₃) δ: 8.40-8.39 (m, 1H), 8.13 (d, *J*= 2.2 Hz, 1H), 4.59 (t, *J*= 5.3 Hz, 2H), 4.38 (t, *J*= 5.3 Hz, 2H), 3.32-3.19 (m, 1H), 2.86 (s, 2H), 1.28 (d, *J*= 6.6 Hz, 6H), 1.12 (s, 9H).

MS (ESI) 376 ($M + H$)⁺.

Step B. 2-(2,2-Dimethylpropyl)-6-(isopropylsulfonyl)-3-[2-(trifluoromethoxy)ethyl]-3H-imidazo[4,5-b]pyridine

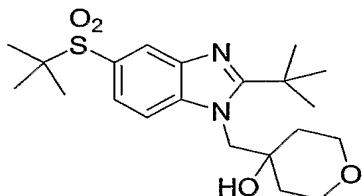
25 The title compound was prepared according to the procedure described in Step B of Example 1 using 2-(2,2-dimethylpropyl)-6-(isopropylthio)-3-[2-(trifluoromethoxy)ethyl]-3H-imidazo[4,5-b]pyridine (Step A) instead of 1-chloro-4-(isopropylthio)benzene.

¹H-NMR (CDCl₃) δ: 8.81 (d, *J*= 2.0 Hz, 1H), 8.47 (d, *J*= 2.0 Hz, 1H), 4.66 (t, *J*= 5.3 Hz, 2H), 4.40 (t, *J*= 5.3 Hz, 2H), 3.35-3.22 (m, 1H), 2.91 (2, 2H), 1.36 (d, *J*= 7.3 Hz, 6H), 1.14 (s, 9H).

30 MS (ESI) 408 ($M + H$)⁺.

Example 51

4-[(2-*tert*-Butyl-5-(*tert*-butylsulfonyl)-1*H*-benzimidazol-1-yl)methyl]tetrahydro-2*H*-pyran-4-ol and its hydrochloride salt

Step A. N-(5-Chloro-2-nitrophenyl)-2,2-dimethylpropanamide

A mixture of 2-nitro-5-chloroaniline (Tokyo Kasei Kogyo Co., Ltd., 3 g, 17.4 mmol), pivaloyl chloride (2.1 mL, 17.4 mmol) and *N,N*-diisopropylethylamine (3.1 mL, 17.4 mmol) in dichloromethane (80 mL) was stirred at room temperature for 20 h. 4-Dimethylaminopyridine (531 mg, 4.4 mmol) was added and the stirring was continued for 3 days. The mixture was poured into water (30 mL) and the mixture was extracted with dichloromethane (30 mL). After removal of solvent, the residue was purified by column chromatography on silica gel (ethyl acetate : hexane = 1 : 20 as eluent) to afford the title compound (1.54 g, 34%) as a pale yellow solid.

- 10 $^1\text{H-NMR}$ (CDCl_3) δ : 10.86 (br, 1H), 9.00 (d, $J= 2.0$ Hz, 1H), 8.21 (d, $J= 9.2$ Hz, 1H), 7.14 (dd, $J= 9.2, 2.0$ Hz, 1H), 1.37 (s, 9H).
- MS (ESI) 255 ($\text{M} - \text{H}$)⁺.

Step B. N-[5-(tert-Butylthio)-2-nitrophenyl]-2,2-dimethylpropanamide

A mixture of *N*-(5-chloro-2-nitrophenyl)-2,2-dimethylpropanamide (Step A, 1.54 g, 6.0 mmol), 2-methyl-2-propanethiol (675 μL , 6.0 mmol) and potassium carbonate (993 mg, 7.2 mmol) in *N,N*-dimethylformamide (25 mL) was stirred in a sealed tube at 100 °C for 17 h. Water (20 mL) was added and precipitate was collected by filtration and dried in vacuo at 50 °C to afford the title compound (1.64 g, 88%) as an orange solid.

- 15 $^1\text{H-NMR}$ (CDCl_3) δ : 10.79 (br, 1H), 9.02 (d, $J= 2.0$ Hz, 1H), 8.14 (d, $J= 8.9$ Hz, 1H), 7.21 (dd, $J= 8.9, 2.0$ Hz, 1H), 1.45 (s, 9H), 1.37 (s, 9H).
- MS (ESI) 309 ($\text{M} - \text{H}$)⁺.

Step C. N-[2-Amino-5-(tert-butylthio)phenyl]-2,2-dimethylpropanamide

The title compound was prepared according to the procedure described in Step E of Example 1 using *N*-(5-(tert-butylthio)-2-nitrophenyl)-2,2-dimethylpropanamide (Step B) instead of *N*-(cyclopropylmethyl)-4-(isopropylsulfonyl)-2-nitroaniline.

- 20 $^1\text{H-NMR}$ (CDCl_3) δ : 7.29 (d, $J= 1.5$ Hz, 1H), 7.22 (dd, $J= 8.1, 1.5$ Hz, 1H), 6.75 (d, $J= 8.1$ Hz, 1H), 3.98 (br., 2H), 1.36 (s, 9H), 1.26 (s, 9H), a peak of NH was not observed.
- MS (ESI) 281 ($\text{M} + \text{H}$)⁺, 279 ($\text{M} - \text{H}$)⁺.

Step D. 2-tert-Butyl-5-(tert-butylthio)-1*H*-benzimidazole

25 To a suspension of sodium hydride (34 mg, 0.86 mmol) in *N,N*-dimethylformamide (1 mL) was added a *N,N*-dimethylformamide solution of *N*-[2-amino-5-(tert-butylthio)phenyl]-2,2-dimethylpropanamide (Step C, 200 mg, 0.71 mmol) at room temperature. After stirring for 30 min, a *N,N*-dimethylformamide solution of 1,6-dioxaspiro[2,5]octane (*Phosphorus and Sulfur and the Related Elements* 1984, **19**, 113-129., 98 mg, 0.86 mmol) was added. The mixture was stirred at room temperature for 3 h and at 100 °C for 5 h. Water (10 mL) was added and the mixture was extracted with ethyl acetate (15 mL). The organic extract was washed with water (5 mL) and brine (5mL) and concentrated. The residue was

purified by pTLC (ethyl acetate : hexane = 1 : 2 as eluent) to afford the title compound as pale brown oil.
MS (ESI) 263 ($M + H$)⁺, 261 ($M - H$)⁻.

Step E. 4-[2-*tert*-Butyl-5-(*tert*-butylthio)-1*H*-benzimidazol-1-yl]methyl]tetrahydro-2*H*-pyran-4-ol and 4-[2-*tert*-butyl-6-(*tert*-butylthio)-1*H*-benzimidazol-1-yl]methyl]tetrahydro-2*H*-pyran-4-ol

5 The mixture of the title compounds was prepared according to the procedure described in Step D using 2-*tert*-butyl-5-(*tert*-butylthio)-1*H*-benzimidazole (Step D) instead of *N*-[2-amino-5-(*tert*-butylthio)phenyl]-2,2-dimethylpropanamide.

MS (ESI) 377 ($M + H$)⁺, 421 ($M + HCOO$)⁻.

Step F. 4-[2-*tert*-Butyl-5-(*tert*-butylsulfonyl)-1*H*-benzimidazol-1-yl]methyl]tetrahydro-2*H*-pyran-4-ol and 4-[2-*tert*-Butyl-6-(*tert*-butylsulfonyl)-1*H*-benzimidazol-1-yl]methyl]tetrahydro-2*H*-pyran-4-ol

10 The mixture of the title compounds was prepared according to the procedure described in Step B of Example 1 using a mixture of 4-[2-*tert*-butyl-5-(*tert*-butylthio)-1*H*-benzimidazol-1-yl]methyl]tetrahydro-2*H*-pyran-4-ol and 4-[2-*tert*-butyl-6-(*tert*-butylthio)-1*H*-benzimidazol-1-yl]methyl]tetrahydro-2*H*-pyran-4-ol (Step E) instead of 15 1-chloro-4-(isopropylthio)benzene. The mixture was purified by HPLC (CHIRALPAK[®] OD-H column, hexane : ethanol : diethylamine = 85 : 15 : 0.1 as eluent) to afford the title compounds.

4-[2-*tert*-Butyl-6-(*tert*-butylsulfonyl)-1*H*-benzimidazol-1-yl]methyl]tetrahydro-2*H*-pyran-4-ol (fraction 1)
retention time: 4.89 min

1*H*-NMR (CDCl₃) δ: 8.27 (s, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.72 (dd, *J* = 7.9, 1.7 Hz, 1H), 4.51 (s, 2H), 3.84-3.77 (m, 2H), 3.71-3.62 (m, 2H), 1.98-1.74 (m, 3H), 1.62 (s, 9H), 1.47-1.42 (m, 2H), 1.36 (s, 9H).
MS (ESI) 409 ($M + H$)⁺, 453 ($M + HCOO$)⁻.

4-[2-*tert*-Butyl-5-(*tert*-butylsulfonyl)-1*H*-benzimidazol-1-yl]methyl]tetrahydro-2*H*-pyran-4-ol (fraction 2)
retention time: 6.97 min

1*H*-NMR (CDCl₃) δ: 8.27 (s, 1H), 7.78-7.68 (m, 2H), 4.48 (s, 2H), 3.86-3.80 (m, 2H), 3.73-3.65 (m, 2H), 1.96-1.70 (m, 3H), 1.61 (s, 9H), 1.50-1.45 (m, 2H), 1.36 (s, 9H).
MS (ESI) 409 ($M + H$)⁺, 453 ($M + HCOO$)⁻.

Step G. 4-[2-*tert*-Butyl-5-(*tert*-butylsulfonyl)-1*H*-benzimidazol-1-yl]methyl]tetrahydro-2*H*-pyran-4-ol hydrochloride salt

27 The title compound was prepared according to the procedure described in Step B of Example 27 using 4-[2-*tert*-butyl-5-(*tert*-butylsulfonyl)-1*H*-benzimidazol-1-yl]methyl]tetrahydro-2*H*-pyran-4-ol (Step F) instead of 2-*tert*-butyl-5-(ethylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazole.

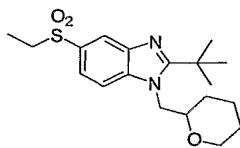
1*H*-NMR (DMSO-d₆) δ: 8.17-8.05 (m, 2H), 7.81-7.73 (m, 1H), 4.62-4.57 (m, 2H), 3.67-3.50 (m, 4H), 1.92-1.78 (m, 2H), 1.61 (s, 9H), 1.34-1.27 (m, 11H), a peak of OH was not observed.

MS (ESI) 409 ($M + H$)⁺, 453 ($M + HCOO$)⁻.

35

Example 52

2-*tert*-Butyl-5-(ethylsulfonyl)-1-(tetrahydro-2*H*-pyran-2-ylmethyl)-1*H*-benzimidazole and its hydrochloride salt



Step A. 4-(Ethylsulfonyl)-2-nitro-N-(tetrahydro-2H-pyran-2-ylmethyl)aniline

The title compound was prepared according to the procedure described in Step A of Example 5 from 1-chloro-4-(ethylsulfonyl)-2-nitrobenzene (step C of Example 2), 2-aminomethyltetrahydropyran

5 (Sciences Chimiques 1972, 3, 685-688) and *N,N*-diisopropylethylamine.

¹H-NMR (CDCl₃) δ: 8.73 (d, J= 2.0 Hz, 1H), 8.69 (br., 1H), 7.84 (dd, J= 9.2, 2.0 Hz, 1H), 6.98 (d, J= 9.2 Hz, 1H), 4.09-4.05 (m, 1H), 3.68-3.29 (m, 4H), 3.12 (q, J= 7.3 Hz, 2H), 1.94-1.39 (m, 6H), 1.30 (t, J= 7.3 Hz, 3H).

MS (ESI) 329 (M + H)⁺, 327 (M - H)⁻.

10 **Step B. 4-(Ethylsulfonyl)-N¹-(tetrahydro-2H-pyran-2-ylmethyl)benzene-1,2-diamine**

The title compound was prepared according to the procedure described in step E of Example 1 using 4-(ethylsulfonyl)-2-nitro-N-(tetrahydro-2H-pyran-2-ylmethyl)aniline (step A) instead of *N*-(cyclopropylmethyl)-4-(isopropylsulfonyl)-2-nitroaniline.

15 ¹H-NMR (CDCl₃) δ: 7.35 (dd, J= 8.4, 2.2 Hz, 1H), 7.17 (d, J= 2.2 Hz, 1H), 6.63 (d, J= 8.4 Hz, 1H), 4.42 (br., 1H), 4.09-4.01 (m, 1H), 3.64-3.45 (m, 4H), 3.28-3.09 (m, 2H), 3.05 (q, J= 7.3 Hz, 2H), 1.97-1.38 (m, 6H), 1.25 (t, J= 7.3 Hz, 3H).

MS (ESI) 299 (M + H)⁺, 297 (M - H)⁻.

Step C. N-{5-(Ethylsulfonyl)-2-[(tetrahydro-2H-pyran-2-ylmethyl)amino]phenyl}-2,2-dimethylpropanamide

The title compound was prepared according to the procedure described in step A of Example 31 using 4-(ethylsulfonyl)-N¹-(tetrahydro-2H-pyran-2-ylmethyl)benzene-1,2-diamine (step B) instead of 4-(ethylsulfonyl)-N¹-[2-(trifluoromethoxy)ethyl]benzene-1,2-diamine.

¹H-NMR (CDCl₃) δ: 7.66-7.63 (m, 2H), 7.08 (br., 1H), 6.72 (d, J= 9.2 Hz, 1H), 4.86-4.83 (m, 1H), 4.03-3.99 (m, 1H), 3.60-3.41 (m, 2H), 3.29-3.21 (m, 1H), 3.14-3.04 (m, 3H), 1.91-1.39 (m, 6H), 1.36 (s, 9H), 1.27 (t, J= 7.3 Hz, 3H).

25 MS (ESI) 383 (M + H)⁺, 381 (M - H)⁻.

Step D. 2-*tert*-Butyl-5-(ethylsulfonyl)-1-(tetrahydro-2H-pyran-2-ylmethyl)-1*H*-benzimidazole

The title compound was prepared according to the procedure described in step B of Example 31 using *N*-{5-(ethylsulfonyl)-2-[(tetrahydro-2H-pyran-2-ylmethyl)amino]phenyl}-2,2-dimethylpropanamide (step C) instead of *N*-(5-(Ethylsulfonyl)-2-[(2-(trifluoromethoxy)ethyl)amino]phenyl)-2,2-dimethylpropanamide.

30 *N*-(5-(Ethylsulfonyl)-2-[(2-(trifluoromethoxy)ethyl)amino]phenyl)-2,2-dimethylpropanamide.

¹H-NMR (CDCl₃) δ: 8.29 (d, J= 1.3 Hz, 1H), 7.74 (dd, J= 8.6, 1.3 Hz, 1H), 7.62 (d, J= 8.6 Hz, 1H), 4.44-4.27 (m, 2H), 3.95-3.89 (m, 1H), 3.76-3.66 (m, 1H), 3.29-3.20 (m, 1H), 3.13 (q, J= 7.6 Hz, 2H), 1.73-1.41 (m, 15H), 1.26 (t, J= 7.6 Hz, 3H).

MS (ESI) 365 (M + H)⁺.

35 **Step E. 2-*tert*-Butyl-5-(ethylsulfonyl)-1-(tetrahydro-2H-pyran-2-ylmethyl)-1*H*-benzimidazole hydrochloride**

The title compound was prepared according to the procedure described in Step B of Example 27 using 2-*tert*-butyl-5-(ethylsulfonyl)-1-(tetrahydro-2H-pyran-2-ylmethyl)-1*H*-benzimidazole (Step D) instead

of 2-*tert*-butyl-5-(ethylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazole.

¹H-NMR (CDCl₃) δ: 8.76 (br., 1H), 7.87-7.78 (m, 2H), 4.65-4.48 (m, 2H), 3.89-3.69 (m, 2H), 3.21-3.11 (m, 3H), 2.05-1.44 (m, 15H), 1.25 (t, J= 7.6 Hz, 3H).

MS (ESI) 365 (M + H)⁺.

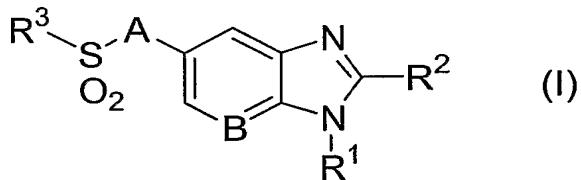
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All publications, including but not limited to, issued patents, patent applications, and journal articles, cited in this application are each herein incorporated by reference in their entirety.

Although the invention has been described above with reference to the disclosed embodiments, those skilled in the art will readily appreciate that the specific experiments detailed are only illustrative of
10 the invention. It should be understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the following claims.

Claims

1. A compound of the formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

5 A represents a bond or $-\text{C}(\text{R}^3)_2-$, wherein each R^3 independently represents a hydrogen atom or a $\text{C}_1\text{-}\text{C}_4$ alkyl group;

B represents a carbon atom or a nitrogen atom;

10 R¹ represents a $\text{C}_1\text{-}\text{C}_4$ alkyl group substituted with 1 to 2 substituents independently selected from the group consisting of a $\text{C}_1\text{-}\text{C}_4$ alkyl group, a hydroxy group, a trifluoromethoxy group, a $\text{C}_1\text{-}\text{C}_4$ alkoxy group, an amino group, a $\text{C}_1\text{-}\text{C}_4$ alkylamino group, a di($\text{C}_1\text{-}\text{C}_4$ alkyl)amino group, a cycloalkyl group, an alkyl-substituted cycloalkyl group, a hydroxy-substituted cycloalkyl group, a heterocyclyl group, an alkyl-substituted heterocyclyl group and a hydroxy-substituted heterocyclyl group;

15 R² represents a cycloalkyl group, an alkyl-substituted cycloalkyl group, a $\text{C}_3\text{-}\text{C}_{10}$ alkyl group, an alkoxy-substituted $\text{C}_3\text{-}\text{C}_{10}$ alkyl group, or a $\text{C}_1\text{-}\text{C}_2$ alkyl group, said $\text{C}_1\text{-}\text{C}_2$ alkyl group being substituted with

20 1 to 2 substituents independently selected from the group consisting of a cycloalkyl group and an alkyl-substituted cycloalkyl group; and

R³ represents an aryl group, a cycloalkyl group, a heterocyclyl group or a $\text{C}_1\text{-}\text{C}_6$ alkyl group, said aryl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a phenyl group, a

25 $\text{C}_1\text{-}\text{C}_4$ alkoxy group, an amino group, a $\text{C}_1\text{-}\text{C}_4$ alkylamino group and a di($\text{C}_1\text{-}\text{C}_4$ alkyl)amino group.

2. The compound or the pharmaceutically acceptable salt, as claimed in claim 1, wherein:

A is a bond;

25 R¹ is a $\text{C}_1\text{-}\text{C}_2$ alkyl group substituted with one substituent selected from the group consisting of a $\text{C}_1\text{-}\text{C}_4$ alkyl group, a hydroxy group, a trifluoromethoxy group, a $\text{C}_1\text{-}\text{C}_4$ alkoxy group, an amino group, a $\text{C}_1\text{-}\text{C}_4$ alkylamino group, a di($\text{C}_1\text{-}\text{C}_4$ alkyl)amino group, a cycloalkyl group, an alkyl-substituted cycloalkyl group, a hydroxy-substituted cycloalkyl group, a heterocyclyl group, an alkyl-substituted heterocyclyl group and a hydroxy-substituted heterocyclyl group; and

30 R² is an alkyl-substituted $\text{C}_3\text{-}\text{C}_6$ cycloalkyl group, a branched $\text{C}_4\text{-}\text{C}_8$ alkyl group, an alkoxy-substituted branched $\text{C}_4\text{-}\text{C}_8$ alkyl group, or a methyl group substituted with one substituent selected from the group consisting of a $\text{C}_3\text{-}\text{C}_5$ cycloalkyl group and an alkyl-substituted $\text{C}_3\text{-}\text{C}_5$ cycloalkyl group.

3. The compound or the pharmaceutically acceptable salt thereof, as claimed in claim 1, wherein:

A is a bond;

35 B is a carbon atom;

R¹ is a $\text{C}_1\text{-}\text{C}_2$ alkyl group substituted with one substituent selected from the group consisting of a $\text{C}_1\text{-}\text{C}_4$ alkyl group, a hydroxy group, a trifluoromethoxy group, a $\text{C}_1\text{-}\text{C}_4$ alkoxy group, an amino group, a

C₁-C₄ alkylamino group, a di(C₁-C₄ alkyl)amino group, a cycloalkyl group, an alkyl-substituted cycloalkyl group, a hydroxy-substituted cycloalkyl group, a heterocycl group, an alkyl-substituted heterocycl group and a hydroxy-substituted heterocycl group;

R² is an alkyl-substituted C₃-C₆ cycloalkyl group, a branched C₄-C₈ alkyl group, an alkoxy-substituted branched C₄-C₈ alkyl group, or a methyl group substituted with one substituent selected from the group consisting of a C₃-C₅ cycloalkyl group and an alkyl-substituted C₃-C₅ cycloalkyl group; and

R³ is a phenyl group, a C₃-C₅ cycloalkyl group or a C₁-C₄ alkyl group, said phenyl group and said alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a C₁-C₄ alkoxy group and a di(C₁-C₄ alkyl)amino group.

4. The compound of claim 1, which is selected from:

1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-(isopropylsulfonyl)-1*H*-benzimidazole; ▾

1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-(ethylsulfonyl)-1*H*-benzimidazole;

15 1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-[(trifluoromethyl)sulfonyl]-1*H*-benzimidazole;

1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-(methylsulfonyl)-1*H*-benzimidazole;

2-(2,2-dimethylpropyl)-5-(isopropylsulfonyl)-1-(2-pyrrolidin-1-ylethyl)-1*H*-benzimidazole;

2-[2-(2,2-dimethylpropyl)-5-(isopropylsulfonyl)-1*H*-benzimidazol-1-yl]-N,N-dimethylethanamine; and

1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-5-(phenylsulfonyl)-1*H*-benzimidazole;

20 or a pharmaceutically acceptable salt thereof.

5. The compound of claim 1, which is selected from:

2-*tert*-butyl-1-(cyclopropylmethyl)-5-(isopropylsulfonyl)-1*H*-benzimidazole;

2-(2,2-dimethylpropyl)-5-(ethylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazole;

25 2-(2,2-dimethylpropyl)-5-(ethylsulfonyl)-1-(tetrahydrofuran-2-ylmethyl)-1*H*-benzimidazole;

4-{[2-(2,2-dimethylpropyl)-5-(isopropylsulfonyl)-1*H*-benzimidazol-1-yl]methyl}tetrahydro-2*H*-pyran-4-ol;

1-{[2-(2,2-dimethylpropyl)-5-(ethylsulfonyl)-1*H*-benzimidazol-1-yl]methyl}cyclopentanol;

2-(2,2-dimethylpropyl)-6-(ethylsulfonyl)-3-(tetrahydro-2*H*-pyran-4-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine;

4-{[2-(2,2-dimethylpropyl)-6-(isopropylsulfonyl)-3*H*-imidazo[4,5-*b*]pyridin-3-yl]methyl}tetrahydro-2*H*-pyran-

30 4-ol;

2-[2-(2,2-dimethylpropyl)-6-(isopropylsulfonyl)-3*H*-imidazo[4,5-*b*]pyridin-3-yl]-N,N-dimethylethanamine;

2-(2,2-dimethylpropyl)-6-(isopropylsulfonyl)-3-(tetrahydro-2*H*-pyran-4-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine;

2-*tert*-butyl-5-[(isopropylsulfonyl)methyl]-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazole;

2-*tert*-butyl-5-(ethylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazole;

35 1-{[2-*tert*-butyl-5-(isopropylsulfonyl)-1*H*-benzimidazol-1-yl]methyl}cyclopentanol; and

2-(2,2-dimethylpropyl)-5-(ethylsulfonyl)-1-[2-(trifluoromethoxy)ethyl]-1*H*-benzimidazole;

or a pharmaceutically acceptable salt thereof.

6. The compound of claim 1, which is selected from:

40 2-{[1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazol-5-yl]sulfonyl}-2-methylpropan-1-ol;

- 1-{{[1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1*H*-benzimidazol-5-yl]sulfonyl}-2-methylpropan-2-ol;
2-{{[2-*tert*-butyl-1-(cyclopropylmethyl)-1*H*-benzimidazol-5-yl]sulfonyl}-2-methylpropan-1-ol; and
1-{{[2-*tert*-butyl-1-(cyclopropylmethyl)-1*H*-benzimidazol-5-yl]sulfonyl}-2-methylpropan-2-ol;
1-{{[2-*tert*-butyl-5-[(2-hydroxy-1,1-dimethylethyl)sulfonyl]-1*H*-benzimidazol-1-yl]methyl)cyclopentanol};
5 2-{{2-(2,2-dimethylpropyl)-1-[2-(trifluoromethoxy)ethyl]-1*H*-benzimidazol-5-yl]sulfonyl}-2-methylpropan-1-ol;
1-{{[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]sulfonyl}-2-methylpropan-2-ol;
2-*tert*-butyl-6-(ethylsulfonyl)-3-(tetrahydro-2*H*-pyran-4-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine;
2-*tert*-butyl-6-(isopropylsulfonyl)-3-(tetrahydro-2*H*-pyran-4-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine;
10 2-(2,2-dimethylpropyl)-6-(ethylsulfonyl)-3-[2-(trifluoromethoxy)ethyl]-3*H*-imidazo[4,5-*b*]pyridine;
2-(2,2-dimethylpropyl)-6-(isopropylsulfonyl)-3-[2-(trifluoromethoxy)ethyl]-3*H*-imidazo[4,5-*b*]pyridine;
4-{{[2-*tert*-butyl-5-(*tert*-butylsulfonyl)-1*H*-benzimidazol-1-yl]methyl}tetrahydro-2*H*-pyran-4-ol; and
2-*tert*-butyl-5-(ethylsulfonyl)-1-(tetrahydro-2*H*-pyran-2-ylmethyl)-1*H*-benzimidazole;
or a pharmaceutically acceptable salt thereof.

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7. A pharmaceutical composition comprising the compound or the pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 6 and a pharmaceutically acceptable carrier.

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8. The pharmaceutical composition as claimed in claim 7 further comprising another pharmacologically active agent.

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9. A method for the treatment of a condition mediated by CB2 receptor activity in a mammalian subject including a human, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of the compound or the pharmaceutically acceptable salt, as claimed in any one of claims 1 to 6.

10. The method as claimed in claim 9, wherein said condition is inflammatory pain, nociceptive pain, neuropathic pain, fibromyalgia, chronic low back pain, visceral pain, acute cerebral ischemia, pain, chronic pain, acute pain, post herpetic neuralgia, neuropathies, neuralgia, diabetic neuropathy,

30 HIV-related neuropathy, nerve injury, rheumatoid arthritic pain, osteoarthritic pain, back pain, cancer pain, dental pain, fibromyalgia, neuritis, sciatica, inflammation, neurodegenerative disease, cough, broncho constriction, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), colitis, cerebrovascular ischemia, emesis such as cancer chemotherapy-induced emesis, rheumatoid arthritis, asthma, Crohn's disease, ulcerative colitis, asthma, dermatitis, seasonal allergic rhinitis, gastroesophageal reflux disease(GERD), constipation, diarrhea, functional gastrointestinal disorder, irritable bowel syndrome, cutaneous T cell lymphoma, multiple sclerosis, osteoarthritis, psoriasis, systemic lupus erythematosus, diabetes, glaucoma, osteoporosis, glomerulonephritis, renal ischemia, nephritis, hepatitis, cerebral stroke, vasculitis, myocardial infarction, cerebral ischemia, reversible airway obstruction, adult respiratory disease syndrome, chronic obstructive pulmonary disease (COPD), cryptogenic fibrosing alveolitis or bronchitis.

INTERNATIONAL SEARCH REPORT

International application No
NL/IB2005/003325

| A. CLASSIFICATION OF SUBJECT MATTER | | | | |
|-------------------------------------|------------|------------|------------|-------------|
| C07D235/08 | C07D401/06 | C07D403/06 | C07D405/06 | C07D413/06 |
| C07D471/04 | A61P37/08 | A61P11/06 | A61P1/04 | A61K31/4184 |
| //(C07D471/04, 235:00, 221:00) | | | | |

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, EMBASE, BIOSIS, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| P, A | WO 2005/030762 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; LIU, ZIPING; MILBURN, CLAIRE;) 7 April 2005 (2005-04-07) claims; examples 17,18,20 ----- | 1-10 |
| A | WO 02/085866 A (ASTRAZENECA AB; CHENG, YUN-XING; TOMASZEWSKI, MIROSLAW; WALPOLE, CHRIS) 31 October 2002 (2002-10-31) cited in the application claims 1,7; table 3; compounds 68,95,96 ----- | 1-10 |
| A | FR 1 481 049 A (LE MINISTRE DES ARMEES, DELEGATION MINISTERIELLE POUR L'ARMEMENT) 19 May 1967 (1967-05-19) page 2, right-hand column, paragraph 2; claim 1; example 2 ----- -/- | 1-10 |

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

14 March 2006

Date of mailing of the international search report

21/03/2006

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Härtinger, S

INTERNATIONAL SEARCH REPORTInternational application No
PCT/IB2005/003325**C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| A | US 4 177 057 A (BELLES, WAYNE S ET AL) 4 December 1979 (1979-12-04) claim 2; example 33 ----- | 1-6 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2005/003325

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 9–10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

| | |
|-------------------------|--|
| national application No | |
| PCT/IB2005/003325 | |

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| | | US 2004116465 A1 17-06-2004 | ZA 200307752 A 03-01-2005 | |
| FR 1481049 | A 19-05-1967 | NONE | | |
| US 4177057 | A 04-12-1979 | CA 1101685 A1 26-05-1981 | | |